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Chronic Cortisol Elevation Induced by Distress: A Vicious Cycle with Morphological and Structural Brain Changes

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Abstract

Chronic stress profoundly affects physical and mental health through complex biochemical and physiological responses. Activation of adrenal glands and the release of cortisol are mainly the key responses throughout this process. Normally, while cortisol regulates inflammation and metabolism, its chronic secretion nevertheless triggers a vicious cycle in four distinct phases.

1st Phase: Prolonged Stress: This phase involves prolonged stress, anxiety, or depression lasting for as long as six or more months, thus triggering persistent and incessant changes in brain's plasticity which causes depressive behaviours due to cortisol dysfunctioning and neurogenical inflammation.

2nd Phase: Hypercortisolemia: Continuous activation of the hypothalamic-pituitary-adrenal's axis leads to elevated cortisol levels, causing glucocorticoid resistance and continuous activation of NF-κB, resulting, therefore, in chronic inflammation.

3rd Phase: Alterations in the Gut Microbiota: Chronic stress and elevated cortisol can also cause dysbiosis as well as increased intestinal permeability, thus allowing microbes to translocate into the bloodstream thus inducing inflammatory responses that can affect the brain, exacerbating neuro-inflammation and causing neuronal damage.

4th Phase: Brain Changes: This phase is characterized by inhibited neurogenesis, excitotoxicity, and brain atrophy, especially in the hippocampus and medial prefrontal cortex, affecting memory and cognitive functions.

Proposed medical interventions include: psychodiagnostic evaluation, psychotherapy, exercise therapy, yoga, Mindfulness and anticortisol medications to circumvent this vicious cycle and improve mental and physical health in people with chronic stress. Chronic stress and hypercortisolemia has proven to cause significant brain alterations. Proper implementation of medical interventions is crucial to halt this vicious cycle, thus improving the overall individuals' health as well as their quality of life.

Keywords: Chronic stress; Anxiety; Depression; Post-traumatic stress disorder

Introduction

If we are to decipher the biggest problem for citizens living in large modern cosmopolitan cities, solving some daily problems at home and at work or the psychopathology that accompany these problems, we would certainly end up choosing the latter. In this review article, we would like to present a functional hypothesis based on scientific articles that could validate our hypothesis. Psychological distress emanating from accelerated modern lifestyles is mainly due to the presence of chronic stress, anxiety, depression, and post-traumatic stress disorder, which could gradually develop over time. One extensively studied oncology example in patients revealed that more than 30 to 50% of cancer patients worldwide experience psychopathological problems each year, making these issues among the most common globally. Although the morbidity of psychopathological complications in patients is very high, they are often inadvertently overlooked. In most of these cases, even if a psychiatrist makes a correct diagnosis, treatment is often not strictly adhered to by the patient or is neglected altogether. Internal stress is a constant stimulus

that also results in a constant increase in cortisol levels. Normally, cortisol, one of the stress hormones, is produced in the adrenal glands. The production of this hormone is controlled by the hypothalamus, and its production is mainly associated with stress or low blood glucocorticoid levels. Cortisol also acts as a neurotransmitter in the brain. Since 1999, brain structures have been studied to highlight whether there are changes in brain structures that may have been attributed to psychological distress caused by chronic stress, which, if prolonged over time, can lead to the development of depression. Several scientists surmise that recent vigorous brain research, will aid psychiatry to recognize the effect of corticosteroids on brain function and the morpho-structural and functional changes that occur thereafter in the brain in relation to the psychopathological changes that occur.

Materials and Methods

This article explores the linkage between psychological distress, high cortisol levels, and all the brain changes that ensue. An extensive literature analysis has recently been conducted using the PubMed database. To explore this, we analysed all article types using the PubMed database, mainly focusing on all data from publications covering the years from 2005 to 2023. The following "MeSH" terms were used in the first PubMed search: chronic stress, cortisol, and neuroplasticity. A second analysis has also been performed by cross-referencing the literature of relevant articles identified in the first search.

Results

Mental and physical health is surely affected by stress, which, if prolonged, generates biochemical and physiological responses in the body. Stress activates the adrenal glands, producing cortisol, a stress hormone. Under normal stress conditions, cortisol decreases inflammation in the body, but during chronic stress, the hypothalamic-pituitary-adrenal (HPA) axis is activated, resulting in excessive cortisol's release and increased inflammation [1]. Elevated cortisol levels activate immune cells, which are highly sensitive to increases in cortisol or glucocorticoids. Glucocorticoids regulate immune cells by binding to specific receptors. Normally, when glucocorticoids bind to their receptors (GR), they activate and move to the nucleus, resulting in repression of inflammatory signaling pathways, including inhibition of NF-κB, a transcription factor crucial for activating pro-inflammatory cytokines [2]. The mechanism of cortisol activation during acute stress determines a greater increase in GR activation, which is more sensitive during elevated cortisol levels. The duration of the interaction between cortisol and GR is generally estimated to be in the neighbourhood of some hours after a single cortisol peak. Eventually, this would result in better control of the body's inflammation. In the case of chronic stress, when elevated cortisol levels remain constant over a long period of time, receptor resistance to glucocorticoid stimuli occurs. This resistance state results in a lower number of GRs and a noticeable decrease in receptor affinity, leading to increased inflammation. The inflammation process begins when NF-κB and its genes are activated. Activated NF-κB will code for pro-inflammatory mediators, initiating the inflammation cascade [2,3]. A meta-analysis study showed the difference in inflammation between patients with depression and the control group without depression. In this scientific study, patients with depression showed increased serum levels of pro-inflammatory cytokines (IL-1β, IL-2, IL-6, IL-12, TNF-α), while very low levels of anti-inflammatory cytokines (IL-4, IL-10, transforming growth factor [TGF]-β1) were revealed [4].

Prolonged elevations of glucocorticoids (GC), such as cortisol, generate: inhibition of neurogenesis in the brain, excitotoxicity, brain atrophy in the hippocampus, specifically in the branching points of the dendrites of CA1 and CA3 regions. High levels of GC could also cause cytoarchitectural damage in the brain [5]. Prolonged elevated cortisol levels for many hours primarily trigger neurodegenerative processes in the hippocampus and prefrontal cortex [6]. In the hippocampus, there is an increase in neuronal death by apoptosis, resulting in a loss of neurons and a decrease in hippocampal volume. This has been observed in rodents, monkeys, humans, and presumably in most other mammals [7] as a direct reaction to perceived environmental stress. The hippocampus, affected by neuronal loss, reduces its capacity for negative feedback control over cortisol release by the adrenal glands, resulting in chronic hypercortisolemia and the so-called cortisol intoxication. In this case, the hippocampus loses its function vis-à-vis stopping cortisol release, and hence its levels remain elevated, causing a lasting systemic self-catabolic potentiation known as the "stress cascade" [5,3]. Acute and chronic stress has proven to have a direct impact on the hippocampus and the medial prefrontal cortex (mPFC) [8]. Studies have shown that the mPFC can decrease the stress response [9]. This has been evidenced in the amygdala, which receives extensive inhibitory collaterals from the prefrontal cortex [10]. Studies on the effects of acute stress have also shown negative effects on cognitive flexibility, attention regulation, and working memory [11]. For example, watching emotionally disturbing movies has been associated with significantly reduced prefrontal cortex activation. Neuroimaging studies have shown that acute stress negatively affects the activation of the brain area related to working memory in the dorsolateral prefrontal cortex [12]. On the other hand, chronic stress leads to dendritic retraction and de-branching in many areas of the mPFC, as observed in rodent and primate models [13-15].

Laboratory rats' studies subjected to high chronic stress levels have shown a significant volumetric reduction in the mPFC.

mPFC's interferes with the ability to suppress the stress response [16]. These volume reductions in the mPFC are limited to the upper layers, where most hippocampal projections end [17]. Both hippocampus and mPFC demostrate dendritic damage associated with chronic stress. Another consequence of chronic stress is a significant decrease in synapse density in various regions of the prefrontal cortex, including the mPFC and the dorsolateral prefrontal cortex. In contrast, there had been no observed dendritic material loss in the infralimbic mPFC neurons projecting to the amygdala in laboratory where rats were subjected to chronic stress [18]. This showed that amygdala neural circuits remain intact/unchanged. Chronic stress increases oxidative stress damage in the body while also reducing the body's antioxidant defense [19,20]. Oxidative stress occurs when oxygen free radicals exceed the capacity of antioxidants to neutralize them [20]. Chronic stress reduces mitochondrial cells function and decreases glutathione (GSH) levels. A study identified GSH level reduction in patients as an indicator of oxidative stress level. Higher oxidative stress correlates with lower GSH levels [21]. Oxidative stress damage has also been identified in the brains of sleep-deprived individuals [22,23]. Hypercortisolemia reduces brain-derived neurotrophic factor (BDNF) expression, thus contributing to induced neuronal damage. Hypercortisolemia causes various inauspicious effects, including morphological and structural changes in the brain [2,3]. Chronic stress is associated with "neuroinflammation" (i.e., activated microglia and astrocytes) and elevated levels of circulating damage-associated molecular patterns (DAMPs), which are endogenous molecules produced by the body under chronic stress. These molecules, similar to oxidative damage, can cause cell's necrosis [2].

In acute stress cases, elevated dopamine levels cause hyperstimulation of dopamine D1 [24,25] receptors, and a decrease in sustained activity and proper coordination of prefrontal cortex neurons. This effect has been observed in humans and other mammals [26]. The same also applies to chronic stress cases. In acute stress cases, while elevated glucocorticoid levels increase short-term dopaminergic transmission in the mesocortical system, prolonged increases in glucocorticoids, as seen in chronic stress, decrease dopaminergic transmission, thus causing similar decreases in sustained activity and proper coordination of prefrontal cortex neurons [16]. This also leads to deterioration and decline in the working memory. This pattern is similar to what is observed in hippocampus-dependent memory. In the hippocampus, there is also an "inverted-U" relationship with stress, where low to moderate stress can improve memory, but chronic stress with elevated glucocorticoid levels can cause a decline in the memory's efficiency. The "inverted-U" details how stress affects working memory: it improves it up to a certain point under low to moderate stress levels, but excessive stress causes significant memory degeneration [25]. The intestine, often referred to as the "second brain," plays a critical role in the connection between stress, neuropsychiatric disorders, and gut health. Stress and these disorders are linked to changes in gut microbiota, which can lead to microbial translocation from the gut into the bloodstream, a phenomenon known as "leaky gut." This process increases the presence of pathogen-associated molecular patterns (PAMPs), which act as inflammatory triggers. Both PAMPs and damage-associated molecular patterns (DAMPs) can activate signalling pathways through Toll-like receptors (TLRs), Nod-like receptor 3 (NLRP3), and immune cells like Caspase-1, ultimately boosting pro-inflammatory cytokine production [2]. These cytokines can then reach the brain, where they activate microglia and astrocytes, contributing to neuroinflammation and affecting brain function (Chronic stress, cortical plasticity, and neuroecology).

Discussion

It is now known that chronic stress definitely and categorically generates continuously high cortisol levels. This has been proven to induce morpho-structural changes in certain parts of the brain's region. The hippocampus, amygdala, and prefrontal cortex are particularly sensitive to these changes thus causing multitude of problems with planning, organizing, memory functioning, recalling abilities, and also in maintaining coherence. Moreover, patients who are suffering from stress have also been found to have troubles finding the right words while thinking, as well as reading new materials, or even with proper orientation.

Patients in such cases describe such brain changes as someone having who have had a stuffed head full of cotton or a "brain fog", which can evidently lead to unwarranted emotional problems. As chronic stress increases, the limbic system starts impeding the flow of information to the cerebral neocortex causing emotional disturbances that ultimately causes acute distress. At this point, the so-called homeostasis between the brainstem, the limbic system and the cerebral cortex is completely lost. Chronic cortisol elevation effects are also manifested through a series of biochemical and physiological responses involving multiple systems of the human body. In this article, we want to theoretically analyse the mechanism through which chronic cortisol secretion could induce a cycle of atypical functions that we could name a vicious cycle (Figure 1). This vicious cycle could theoretically consist of four phases (Figure 1).

1st Phase

The first phase of this vicious cycle starts with an overwhelmingly incessant sense of stress, anxiety, or even long-term depression lasting for as long as six months or sometimes even more [26]. During this prolonged stress period, the body's hypothalamic-pituitary-adrenal (HPA) axis is in constant

agitation, resulting in relentless secretion of cortisol, a condition known as hypercortisolemia. This unabated elevation of cortisol sets the stage for a cascade of health issues, illustrating the body's struggle to cope with continuous stress and its profound repercussions.

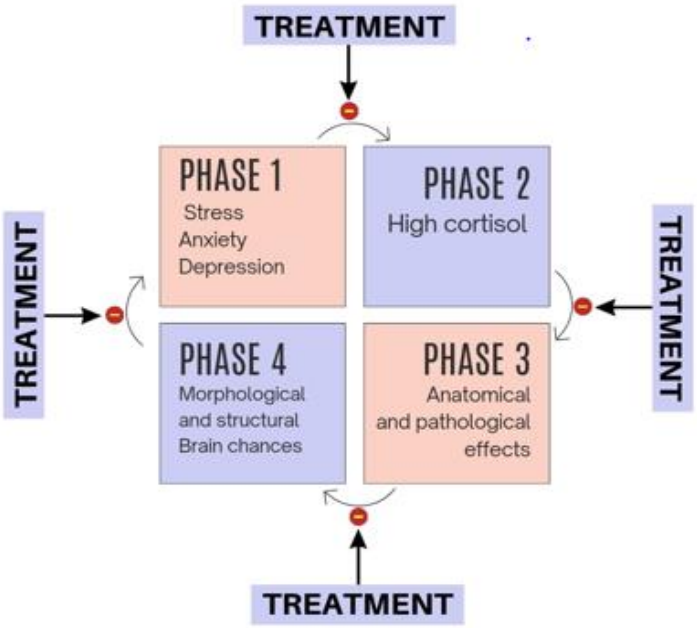

Figure 1: *Stress, anxiety and depression if continues uninterrupted will establish a vicious cycle.*

2nd Phase

The second phase of this vicious cycle, shifts focus to the body's predisposition for inflammation control and the overall body health [1]. Hypercortisolemia, which is marked by elevated cortisol levels, triggers immune cells which are highly sensitive to glucocorticoids. Under normal conditions, glucocorticoids bind to their specific receptors (GR) and suppress inflammatory signalling pathways by inhibiting the transcription factor NF-κB, which is crucial for activating proinflammatory cytokines [2]. This suppression is the way how glucocorticoids exert their therapeutic effects, by reducing inflammatory mediators and regulating the immune system's response [3]. Prolonged hypercortisolemia also leads to a self-resistance development in glucocorticoid receptors, thus reducing both their numbers and their affinity. This resistance causes a continuous activation of NF-κB, thus triggering a cascade of chronic inflammation [3,4]. Essentially, sustained stress inhibits the body's immune function, leading, among other things, to persistent inflammation and health deterioration.

3rd Phase

The third phase of this cycle (Figure 1), starts to exhibit both anatomical and pathological effects which become even more evident (Figure 2). At this stage, diagnosing chronic stress and implementing a therapeutic regimen for secondary prevention becomes crucially necessary. One significant pathological condition observed at this phase is the alteration of the intestinal microbiota. Elevated cortisol levels under chronic stress can also lead to dysbiosis, an imbalance in the gut microbiota, aggravating further the vicious cycle of stress and expediting health deterioration. This imbalance can increase intestinal permeability, a phenomenon known as "leaky gut". Greater intestinal permeability allows for the translocation of microbes and their agents (pathogen-associated molecular patterns, PAMPs) into the bloodstream. These PAMPs can induce an inflammatory response by activating Toll-like receptors (TLRs) and Nod-like receptor 3 (NLRP3) in the immune cells, thereby increasing the production of pro-inflammatory cytokines. These pro-inflammatory cytokines can even reach the brain and activate microglia and astrocytes, which in turn could lead to the exacerbation of neuro-inflammation which causes neuronal damage, a subject that will be discussed underneath [3,27]. This process permeates the vicious cycle of chronic stress, inflammation, and neuronal damage, thus causing inauspicious effects on the physical and mental health of the individual. Hypercortisolemia can also affect the Cancer tumour microenvironment; cortisol and other stress hormones can modify the tumor's immune function environment, thus promoting cancer growth or even metastasis. Chronic stress has also been discerned to increase the expression of genes associated with infiltration and metastasis into the cancer cells, as well as weakening the immune response against cancer [28]. These effects can largely be mitigated through the activation of signalling pathways such as the epidermal growth factor (EGF) and mitogen-activated protein kinase (MAPK) pathways [29]. Moreover, elevated cortisol levels were found to cause alterations in cytokine signalling in the tumour microenvironment. Studies have shown that stress can elevate the production of pro-inflammatory cytokines such as IL-6 and TNF-α in the tumour environment, which could in turn promote angiogenesis and tumour growth [30]. These effects may be particularly important in breast cancer cases, where it has been noted that chronic stress could increase instances of metastasis by modifying the blood-brain barrier and promoting cancer cell infiltration [31]. Furthermore, oncological studies in patients have found that chronic stress can modify the tumor microenvironment through immunosuppression and inflammation, thus affecting inauspiciously cancer progression [32]. The relationship between stress and cancer not only involves the immune changes but also alterations in cell signalling and gene expression that can affect

the proliferation and metastasis of cancer cells [33,34]. Chronic stress and elevated cortisol levels are also implicated in numerous pathologies, each of which significantly affecting the human health, and more importantly, the quality of live, as illustrated in (Figure 2).

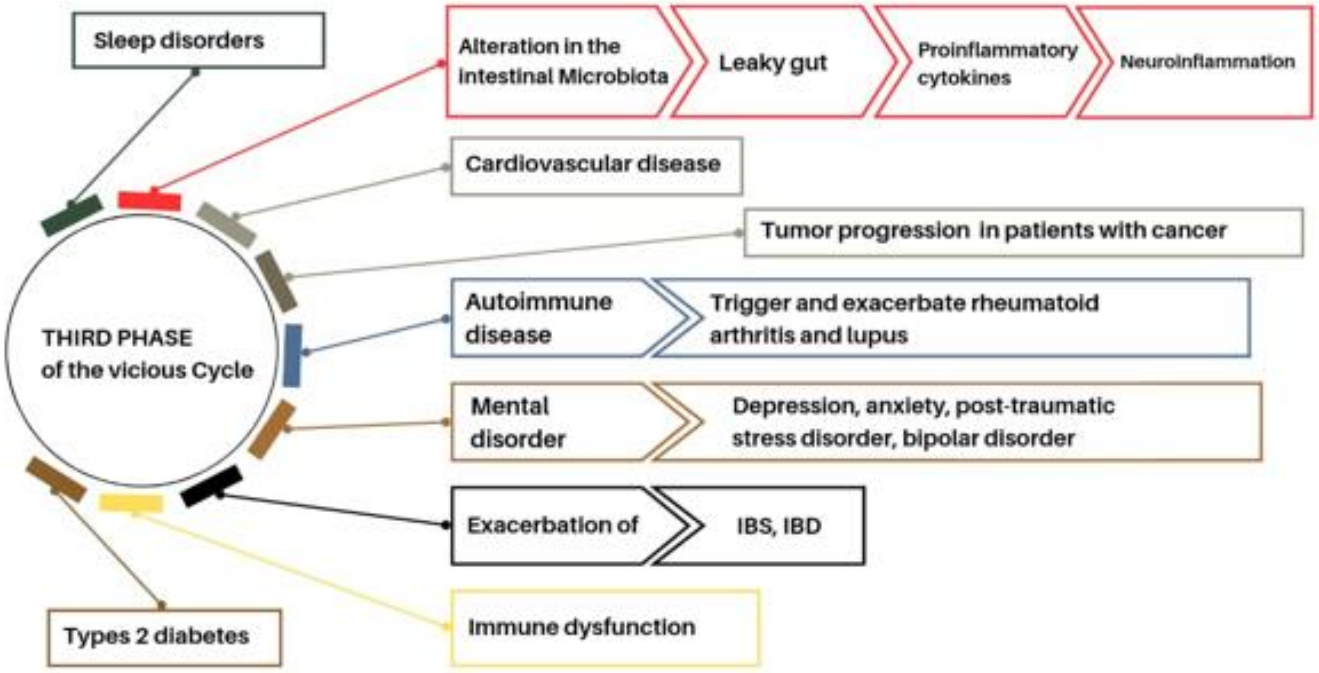

Figure 2: *Pathological Effect of the Third Phase of the Vicious Cycle.*

Cardiovascular Disease: Chronic stress has been linked to a higher risk of cardiovascular disease. Research from the European Journal of Preventive Cardiology (2017) and the American Heart Association [35] have shown that elevated cortisol can lead to higher blood pressure and arterial plaque build-up.

Type 2 Diabetes: A 2018 longitudinal study published in Diabetes Care, found a significant link between perceived stress and the risk of type 2 diabetes in middle-aged adults [36].

Gastrointestinal Disorders: Chronic stress have also been found to exacerbate gastrointestinal issues like irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), as noted by Ge [37].

Obesity: Elevated cortisol from chronic stress could also lead to unwarranted abdominal fat accumulation, a key risk factor for obesity and related metabolic disorders [19]. Stress can also disrupt cognitive functions such as self-regulation and promote unhealthy behaviors such as overeating, particularly in consumed foods that have high-calories, fatty, and sugary ingredients [38].

Sleep Disorders: Stress have also been shown to negatively impact sleep quality patterns. Research by Kalmbach [39] discusses the concept of sleep pathogenic reactivity, which relates to an individual's susceptibility to stress-related sleep disorders.

Mental Health Issues: Chronic stress has been found to cause severe mental disorder namely: depression, anxiety, PTSD, and bipolar disease, as documented in the Journal of Affective Disorders [40].

Immune Dysfunction: Everyday stress, on the other hand can significantly limit the immune function and negatively impact individual's overall health. Seiler [41] explored this unique relationship, while Castellani [42] highlighted the close physical and functional communication between the brain and the immune system, revealing new pathways for brain-immune interactions.

Autoimmune Diseases: Chronic stress, have also been found to trigger or worsen autoimmune diseases like rheumatoid arthritis and lupus [43] study of a Swedish cohort revealed a significant association between stress-related disorders and increased risk of autoimmune diseases, emphasizing the need for effective stress management treatment and hence prevention.

The above findings have come to underscore the profound impact of chronic stress on multiple aspects of health. It also came to highlight the immediate need for effective stress management strategies to either mitigate these risks, or even eradicate them altogether. This scientific evidence supports the link between chronic stress and a variety of health conditions, thus providing a more comprehensive understanding of the various effects of stress

on the body and mind through the different phases of this vicious and incessant "vicious cycle".

4th Phase

The fourth phase of the vicious cycle (Figure 1) is marked by profound structural and functional changes in the brain, including the inhibition of neurogenesis, excitotoxicity, and brain atrophy. Notably, the hippocampus, a critical region for memory and learning, experiences significant gradual neuronal loss and reduced volume [5,3]. Excitotoxicity refers to cellular damage caused by the overstimulation of glutamate receptors in the nerve cells. While glutamate is essential for neurotransmission, excessive amounts, though, could unnecessarily lead to neuronal death. This phenomenon is manifested in various neurodegenerative conditions following brain injuries, which contribute to a significant disease progression. In the context of chronic hypercortisolemia, the overstimulation of glutamate receptors in the hippocampus is particularly detrimental. The hippocampus is highly sensitive to cortisol due to its dense concentration of glucocorticoid receptors. Elevated cortisol levels have shown to trigger excessive glutamate release, leading to excitotoxicity and neuronal death, which adversely impacts memory and learning [5]. Furthermore, chronic stress and elevated cortisol disrupt synaptic plasticity by altering gene expression and inhibiting the formation of new neuronal connections. This impairment of neuroplasticity in the hippocampus not only hampers memory and learning abilities, but also exacerbates the structural damage, thus creating a feedback loop that leads to cognitive decline [3]. These changes have found to have significant implications on cognitive function, as neuroplasticity is essential for learning, memory, and adaptability to new environments. Hence, impaired neuroplasticity due to excitotoxicity and hypercortisolemia may lead to cognitive deficits and could hinder the brain's ability to adapt and respond to environmental challenges, underscoring the need for speedy proactive stress management strategies. The cytoarchitectural changes compromise hippocampus's ability of regulating cortisol release, perpetuating high cortisol levels and worsening neurodegeneration [5]. Besides the hippocampus, the medial prefrontal cortex (mPFC) have also been found to be vulnerable to elevated cortisol. Studies on rodents and primates have shown that hypercortisolemia causes dendritic retraction and disorganization in the mPFC, thus impairing stress response suppression and leading to cognitive dysfunction [11-15]. This damage affects working memory, attention focusing, in addition to other cognitive functions [16].

Chronic stress, have also been found to reduce synaptic density in the prefrontal cortex. Experiments on rats revealed a significant decrease in the volume of mPFC, especially in areas where hippocampal projections ends [17]. This synaptic density reduction impacts cognitive flexibility and attention [18]. Moreover, hypercortisolemia lowers brain-derived neurotrophic factor (BDNF) expression, thus exacerbating neuronal damage and cognitive impairment [44,45]. Acute and chronic stress affects the brain in various ways. For instance, short-term stress can enhance working memory and cognitive functions by increasing dopaminergic transmission, whereas prolonged glucocorticoid levels decrease this transmission, thus impairing sustained activity and coordination in the prefrontal cortex [16,25]. Increased microglial and astrocyte activation, along with elevated damage-associated molecular patterns (DAMPs), could also lead, among other things, to cell necrosis [2]. Neuroinflammation, triggered by immune cell activation and oxidative stress, releases proinflammatory cytokines, causing significant neuronal damage [46]. Gut microbiota changes could also impact neurotransmitter and neuroactive metabolite production. These metabolites influence neuroinflammation, the blood-brain barrier, and neuronal signaling, exacerbating in their way chronic stress effects on the brain [47].These metabolites can affect neuroinflammation, the blood-brain barrier and neuronal signalling, inauspiciously affecting the brain's chronic stress. Understanding these mechanisms underscores the critical impact of chronic stress on brain's health and the urgent need for early intervention which is paramount for stress management to halt long-term neurological damage.

Managing hypercortisolemia with proper medical intervention have also been found to halt this harmful cycle (Figure 1). The interplay between stress, inflammation, and gut microbiota offers promising conduits for mitigating, or even eradicating, chronic stress. For instance, probiotics, prebiotics, and specific forms of diets could help restore microbial balance and reduce inflammation [27]. Dietary strategies like the Mediterranean diet, which is rich in fiber, antioxidants, and omega-3 fatty acids, have shown to have significant benefits for mental health and inflammation reduction [48]. Nutritional supplements like omega-3 fatty acids, antioxidants, B vitamins, zinc, and magnesium aid neurotransmitter signalling and help protect mitochondrial function. Additionally, regular physical activity such as yoga and Mindfulness could enhance life's quality by improving sleep patterns and inhibiting elevated cortisol levels. Research done have indicated that previously sedentary older adults who engaged in daily walking for six months to up to a year have exhibited increased hippocampal size, most likely due to enhanced neurogenesis in the dentate gyrus affected by rigirous exercise and enriched environments [49]. Psychodiagnostic assessment and psychotherapy are hence crucial for patients who suffer from chronic stress who are called upon to reduce cortisol levels [50,51]. Finally, medications such as serotonin and norepinephrine reuptake inhibitors, glucocorticoid modulators, and CRH antagonists may also help reduce cortisol levels.

Conclusions

Various scientific reviews have summarized and integrated materials relating to the relationships between physiological and psychosocial stress, the stress hormone cortisol, regulated by the HPA axis, and the morpho-structural changes that stress produces in the brain. Chronic psychological stress has been shown to lead to increased cortisol levels in the body, causing morphological, structural, and functional alterations at the cerebral level. Hypercortisolemia can cause changes in the brain, leading to loss of neuroplasticity and episodic memory, thus forming the ideal conditions for the development of neurodegenerative diseases and cancer. We conclude that the implementation of medical intervention measures is crucial for halting this rather treatable vicious cycle (Figure 1). Chronic stress has shown to have profound and multifaceted effects on human health, impacting not only the immune response and inflammation, but also the structure and function of the brain. Understanding these mechanisms is fundamental for developing effective interventions that helps in the mitigation, or even probably eradication, of the adverse effects of chronic stress. Strategies that regulate the stress response, improve psychological resilience, and restore microbial balance have proven to be highly effective in addressing the adverse consequences of chronic stress and hence help improving the overall human's health. Additional studies on the therapeutic effect of these medical interventions in patients with chronic stress could empirically confirm our vicious cycle hypothesis (Figure 1). Applying these interventions to patients with chronic stress could comprehensively and multidimensionally improve their health, leading to a significant enhancement in their quality of life. We suggest that future research should focus on randomized scientific studies and brain autopsies to empirically examine the medical consequences of chronic hypercortisolemia. Additionally, exploring the impact of integrated approaches such as the Mediterranean diet, regular physical activity, yoga, and specific nutritional supplements could provide a solid foundation for new therapeutic strategies. Stress is a modifiable risk factor, and growing evidence suggests that effective managing of stress levels have yielded significant benefits for human's psychological and physical health. In summary, combating the devastating effects of chronic stress requires deep understanding of its mechanisms and a holistic treatment approach, combining medical interventions, psychological therapies, and lifestyle changes to restore balance and overall health in affected individuals.

References

1. Hassamal S. Chronic stress, neuroinflammation, and depression: an overview of pathophysiological mechanisms and emerging anti-inflammatories. Front Psychiatry. 2023; 11: 1130989.
2. Bauer ME, Teixeira AL. Inflammation in psychiatric disorders: what comes first? Ann N Y Acad Sci. 2019; 1437: 57-67.
3. Reser JE. Chronic stress, cortical plasticity and neuroecology. Behav Processes. 2016; 129: 105-115.
4. Osimo EF, Pillinger T, Rodriguez IM, Khandaker GM, Pariante CM, Oliver D. Howes Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain Behav Immun. 2020; 87: 901-909.
5. Sapolsky RM. Why stress is bad for your brain. Sci. 1996; 273: 749-50.
6. Kim JJ, Yoon KS. Stress: metaplastic effects in the hippocampus. Trends Neurosci. 1998; 21: 505-509.
7. Lambert KG, Gerecke KM, Quadros PS, Doudera E, Jasnow AM, Kinsley CH. Activity-stress increases density of GFAP-immunoreactive astrocytes in the rat hippocampus. Stress. 2000; 3: 275-284.
8. Cerqueira JJ, Mailliet F, Almeida OF, Jay TM, Sousa N. The prefrontal cortex as a key target of the maladaptive response to stress. J Neurosci. 2007; 27: 2781-2787.
9. Figueiredo HF, Bodie BL, Tauchi M, Dolgas CM, Herman JP. Stress integration after acute and chronic predator stress: differential activation of central stress circuitry and sensitization of the hypothalamo-pituitary-adrenocortical axis. Endocrinol. 2003; 144: 5249-5258.
10. Radley JJ, Morrison JH. Repeated stress and structural plasticity in the brain. Ageing Res Rev. 2005; 4: 271-287.
11. Luethi M, Meier B, Sandi C. Stress effects on working memory, explicit memory, and implicit memory for neutral and emotional stimuli in healthy men. Front Behav Neurosci. 2009; 2: 5.
12. Qin S, Hermans EJ, van Marle HJ, Luo J, Fernandez G. Acute psychological stress reduces working memory-related activity in the dorsolateral prefrontal cortex. Biol Psychiatry. 2009; 66: 25-32.
13. Finsterwald C, Alberini CM. Stress and glucocorticoid receptor-dependent mechanisms in long-term memory: from adaptive responses to psychopathologies. Neurobiol Learn Mem. 2014; 112: 17-29.
14. Brown ES, Vera E, Frol AB, Woolston DJ, Johnson B. Effects of chronic prednisone therapy on mood and memory. J Affect Disord. 2007; 99: 279-283.
15. Liston C, Miller MM, Goldwater DS, Radley JJ, Rocher AB, Hof PR, Morrison JH, McEwen BS. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J Neurosci. 2006; 26: 7870-7874.
16. Mizoguchi K, Yuzurihara M, Ishige A, Sasaki H, Chui DH, Tabira T. Chronic stress induces impairment of spatial working memory because of prefrontal dopaminergic dysfunction. J Neurosci. 2000; 20: 1568-1574.
17. Jay TM, Witter MP. Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin. J Comp Neurol. 1991; 313: 574-586.
18. Shansky RM, Morrison JH. Stress-induced dendritic remodeling in the medial prefrontal cortex: effects of circuit, hormones and rest. Brain Res. 2009; 1293: 108-113.

19. Aschbacher K, O'Donovan A, Wolkowitz OM, Dhabhar FS, Su Y, Epel E. Good stress, bad stress and oxidative stress: insights from anticipatory cortisol reactivity. Psychoneuroendocrinol. 2013; 38: 1698-1708.
20. McIntosh LJ, Cortopassi KM, Sapolsky RM. Glucocorticoids may alter antioxidant enzyme capacity in the brain: kainic acid studies. Brain Res. 1998; 791: 215-222.
21. Presnell CE, Bhatti G, Numan LS, Lerche M, Alkhateeb SK, Ghalib M, et al. Computational insights into the role of glutathione in oxidative stress. Curr Neurovasc Res. 2013; 10: 185-194.
22. Atrooz F, Salim S. Sleep deprivation, oxidative stress and inflammation. Adv Protein Chem Struct Biol. 2020; 119: 309-336.
23. Bin Heyat MB, Akhtar F, Sultana A, Tumrani S, Teelhawod BN, Abbasi R, et al. Role of oxidative stress and inflammation in insomnia sleep disorder and cardiovascular diseases: herbal antioxidants and anti-inflammatory coupled with insomnia detection using machine learning. Curr Pharm Des. 2022; 28: 3618-3636.
24. Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat Neurosci. 2007; 10: 376-384.
25. Gibbs SE, D'Esposito M. A functional MRI study of the effects of bromocriptine, a dopamine receptor agonist, on component processes of working memory. Psychopharmacol (Berl). 2005; 180: 644-653.
26. Knezevic E, Nenic K, Milanovic V, Nick Knezevic N. The role of cortisol in chronic stress, neurodegenerative diseases, and psychological disorders. Cells. 2023; 12: 2726.
27. Chudzik A, Orzylowska A, Rola R, Greg J. Stanisz. Probiotics, prebiotics and postbiotics on mitigation of depression symptoms: modulation of the brain–gut–microbiome Axis. Biomolecules. 2021; 11: 1000.
28. Lutgendorf SK, Sood AK, Antoni MH. Host factors and cancer progression: bio behavioral signaling pathways and interventions. J Clin Oncol. 2010; 28: 4094-4099.
29. McDougall AR, Tolcos M, Hooper SB, Cole TJ, Wallace MJ. Trop2: from development to disease. Dev Dyn. 2015; 244: 99-109.
30. Armaiz-Pena GN, Lutgendorf SK, Cole SW, Sood AK. Neuroendocrine modulation of cancer progression. Brain Behav Immun. 2009; 23: 10-15.
31. Herrera RA, Deshpande K, Martirosian V, Saatian B, Julian A, Eisenbarth R, et al. Cortisol promotes breast-to-brain metastasis through the blood-cerebrospinal fluid barrier. Cancer Rep (Hoboken). 2022; 5: e1351.
32. Pena-Vargas C, Armaiz-Pena G, Castro-Figueroa E. A biopsychosocial approach to grief, depression, and the role of emotional regulation. Behav Sci (Basel). 2021; 11: 110.
33. Zheng L, Qin S, Si W, Wang A, Xing B, Gao R, et al. Pan-cancer single-cell landscape of tumor-infiltrating T cells. Sci. 2021; 374: abe6474.
34. Dai S, Mo Y, Wang Y, Xiang B, Liao Q, Zhou M, et al. Chronic stress promotes cancer development. Front Oncol. 2020; 10: 1492.
35. Kivimaki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. Nat Rev Cardiol. 2018; 15: 215-229.
36. Hackett RA, Steptoe A. Type 2 diabetes mellitus and psychological stress - a modifiable risk factor. Nat Rev Endocrinol. 2017; 13: 547-560.
37. Ge L, Liu S, Li S, Yang J, Hu G, Xu C, et al. Psychological stress in inflammatory bowel disease: Psychoneuroimmunological insights into bidirectional gut-brain communications. Front Immunol. 2022; 13: 1016578.
38. Kumar R, Rizvi MR, Saraswat S. Obesity and stress: a contingent paralysis. Int J Prev Med. 2022; 13: 95.
39. Kalmbach DA, Anderson JR, Drake CL. The impact of stress on sleep: Pathogenic sleep reactivity as a vulnerability to insomnia and circadian disorders. J Sleep Res. 2018; 27: e12710.
40. Davis MT, Holmes SE, Pietrzak RH, Esterlis I. Neurobiology of chronic stress-related psychiatric disorders: evidence from molecular imaging studies. Chronic Stress (Thousand Oaks). 2017; 1: 2470547017710916.
41. Annina Seiler: Stress challenges and immunity in space, from mechanisms to monitoring and preventive strategies. Author: Alexander Chouker, 2nd edition. Springer. 2020; 71-92.
42. Castellani G, Croese T, Peralta Ramos JM, Schwartz M. Transforming the understanding of brain immunity. Sci. 2023; 380: eabo7649.
43. Song H, Fang F, Tomasson G, Arnberg FK, Mataix-Cols D, Fernandez de la Cruz L, Almqvist C, Fall K, Valdimarsdottir UA. Association of stress-related disorders with subsequent autoimmune disease. JAMA. 2018; 319: 2388-2400.
44. Azoulay D, Lavie D, Horowitz N, Suriu C, Gatt ME, Akria L, Perlman R, Braester A, Ben-Yehuda D. Bortezomib-induced peripheral neuropathy is related to altered levels of brain-derived neurotrophic factor in the peripheral blood of patients with multiple myeloma. Br J Haematol. 2014; 164: 454-456.
45. McEwen BS, Gray JD, Nasca C. 60 YEARS OF NEUROENDOCRINOLOGY: Redefining neuroendocrinology: stress, sex and cognitive and emotional regulation. J Endocrinol. 2015; 226: T67-83.
46. Leonard BE. Inflammation and depression: a causal or coincidental link to the pathophysiology? Acta Neuropsychiatr. 2018; 30: 1-16.
47. Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. Nat Neurosci. 2017; 20: 145-155.
48. Casas R, Estruch R, Sacanella E. Influence of bioactive nutrients on the atherosclerotic process: A Review. Nutrients. 2018; 10: 1630.
49. Erickson KI, Miller DL, Roecklein KA. The aging hippocampus: interactions between exercise, depression, and BDNF. Neuroscientist. 2012; 18: 82-97.
50. Fritzsche K, Burger T, Hartmann A, Nubling M, Spahn C. The psychosocial evaluation of medically-ill inpatients - accordance between mental disorders and self-rated psychosocial distress. Psychosoc Med. 2005.