EC PSYCHOLOGY AND PSYCHIATRY
Mini Review

Hippocampus, HPA-axis, and Covid-19: Medical Student Stress and Interventional Strategies

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Abstract

Medical training is one of the most challenging times along the journey of a future health care professional. Lack of awareness of the stressors involved and the coping strategies can debilitate a student's capability to carry out efficient and effective stress management strategies, turning medical school into an uphill battle. The recent pandemic (Covid-19) that has practically dictated our day-to-day activities over the past year has introduced novel stressors for the general population, including those pursuing a medical education and working in a healthcare profession. Stress generally induces an imbalance in homeostasis; but, if the stress is prolonged, its cumulative effects can result in changes that negatively affect tissues and organ systems (allostatic overload). Effects of stress on the HPA-axis and its regulation through the hippocampus serves as a window for further investigation into the link between cortisol and hippocampal plasticity. This holds significant value for students, particularly those pursuing a healthcare profession. Lastly, we list several coping-strategies for current medical students based on neurobiological research evidence to effectively manage stress.

Keywords: *Hippocampus; Hypothalamus-Pituitary Axis; Neuroplasticity; Covid-19; Medical Students; Stress; Cortisol*

Introduction

Medicine is an intrinsically demanding profession. Future medical professionals are not in an optimal state of health during their medical training [1]. Some of the stressors that are responsible for this have been described in scientific literature for several years [2]. When compared to the general population, medical students experience higher levels of depression [3] and anxiety [4]. These findings further suggest the notion of medical student "burnout" - a measure of distress involving emotional exhaustion and a low sense of personal accomplishment [5].

Stress and Covid-19

With implementation of the required social distancing, closure of education sector, limitations on travelling, and other related inconvenience, the Covid-19 pandemic has truly taken over one's day-to-day functioning [6]. General stressors could range across times of transition such as preparing for licensing exams and beginning clerkships, physical challenges such as the amount of hours required during clerkship and/or basic sciences and individual stressors such as death in family and/or divorce [7]. Students across the globe are now facing novel stressors due to the introduction of Covid-19, no matter their background in training, and medical students are displaying a deterioration in their studies and work performance [8]. This feeling of anxiety and concern could lead our future healthcare professionals to raise legitimate concerns regarding their graduation and fears of returning to normal [9].

Stress and neurobiology

Chronic exposure to the same stress attenuates dopamine (DA) release in the ventral striatum, increases turnover of norepinephrine (NE) in terminal projection areas of nucleus coeruleus, increases NE in the hippocampus, downregulates expression of 5-hydroxy-trymptamine receptor 1A (5-HT_{1A}) in the hippocampus, and elevates nitric oxide (NO) production in the brain [10-13]. In case of a challenge or stress, the body attempts to cope with the situation-at-hand, which involves the enhanced activity of the hypothalamus-pituitary-axis (HPA) [14]. Stress-induced-NE-release in the hippocampus and amygdala is also shown to induce HPA-axis activity, which is followed by a secretion of cortisol (glucocorticoid) from the adrenal cortex that triggers physiological and behavioural responses aimed at our homeostasis [15,16].

Stress and the hippocampus

It has been shown that the largest content of Type 1 and Type 2 corticosteroid receptors in the brain is located in the hippocampus. Moreover, Type 1 hippocampal receptors are shown to be linked with basal (circadian) Hypothalamus-Pituitary axis (HPA-axis) regulation [17]. In fact, bilateral and unilateral hippocampal damage has been shown to abolish the awakening-cortisol-response, an otherwise common phenomena among healthy adults [18]. Thus, hippocampus has a unique and important role in the HPA-axis and cortisol release. Adrenal steroids (ex: glucocorticoids) can lead to a stress-induced atrophy of apical CA3 dendrites in the hippocampus, which could lead to cognitive impairment in learning and short-term memory tasks [19]. Hippocampus exhibits an enhanced sensitivity to cortisol, and a chronic elevation of glucocorticoids (Cushing Syndrome) is found to be associated with deficits in concentration and memory [20]. Further, frequent cortisol elevations have also been linked with temporal lobe atrophy and reduced declarative/episodic memory performance among flight attendants [21].

Stress and the HPA-axis

A dysregulation in the HPA plays a critical role in sleep disorders, such as insomnia [22]. This is especially concerning for our future healthcare providers as academic performance is positively correlated with sleep schedule regularity [23]. In one study, researchers found that an altered profile of diurnal cortisol levels (lower than normal cortisol output in the morning and a higher than normal output in the evening) is correlated with depressive symptoms [24]. This suggests that it is critical for students, particularly in medicine, as well as healthcare professionals to bring their HPA-dysfunction back to normal. Although stress is shown to improve working memory among students, it only upholds its value up to a certain point (fine line between allostatic load and overload) [25]. In a study looking at medical staff in Wuhan, China during the heart of the epidemic, researchers found that the caregivers were exposed to stressful conditions every day such as facing a patient's worsening condition, or even, death - a state of high psychological stress [26]. Thus, it is critical for students to learn habits of self-care in order to provide care for others as future caregivers themselves [27] (Figure 1).

Stress and neuroplasticity

Plasticity is the capacity of neural activity to modify neural circuitry. Synaptic plasticity is the ability of synaptic transmission to incorporate transient changes into memory traces [28]. Hippocampus undergoes synaptic remodeling in early Alzheimer's Disease (AD), displaying its plastic capability [29]. Hippocampus is associated with bidirectional plasticity in the form of long-term potentiation (LTP), which is the consolidation of synaptic strength, and long-term depression (LTD), which is the weakening of synaptic strength [30,31]. As mentioned previously, stress affects the hippocampus, which in turn can have its deleterious effects on memory acquisition and consolidation.

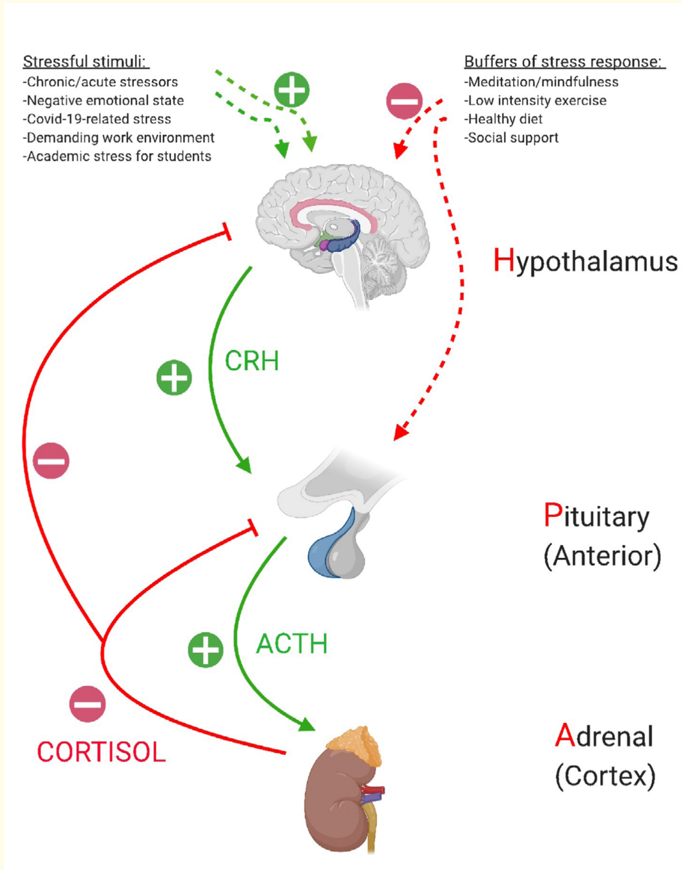

Figure 1: *The HPA Axis. Stress levels are perceived in the brain. Hippocampus activates the stress system by triggering the hypothalamus to release corticotropin-releasing hormone (CRH) into the anterior pituitary. Adrenocorticotropic hormone (ACTH) is released by the anterior pituitary which travels to the adrenal cortex via the bloodstream. Zona fasciculata (ZF) of the adrenal cortex releases the glucocorticoid cortisol that acts as a negative feedback modulator for hippocampal, hypothalamic, and anterior pituitary involvement in the stress response. The green arrows show positive feedback, while the red arrows indicate negative feedback effects. Created with BioRender.com*

Stress management

Students who reported a wider array of active engagement in self-care activities experienced a higher quality of life and less stress in general [32]. A report out of Vanderbilt School of Medicine, Nashville, Tennessee suggests a comprehensive wellness objective to combat medical student stress [7]. Suggested interventions include Mentoring activities (time management and study skills), Mindfulness activities (meditation classes and student discussion blogs), Body health workshops (nutritional and sleep information sessions), Social activities (exam study breaks and volunteer study events), and Community-based activities (farmer's market and recycling initiatives). These interventions are of significance since it is well-known that social-support relationships are positively related to cognitive functioning [33]. As summarized by Ozbay and colleagues, tasks such as mental arithmetic and public speaking cause a significantly smaller rise in blood cortisol in those who are socially supported compared to those who are not [34]. It is also necessary for medical students to engage in conversation with other healthcare professionals and/or faculty regarding stress-preventative services/strategies where they are able to discuss the various stressors in their journey, and how they can process conflict and nurture self-awareness [35-37].

Meditation is shown to be comparable to other relaxation techniques in reducing anxiety and stress associated with several mental and physical disorders [38,39]. Research from 2018 concluded that upon yoga and meditation lifestyle intervention, subjects had a significant decrease in their blood cortisol, IL-6, and ROS levels, suggesting the neuroplastic and stress-alleviating benefits of meditation [40]. Low, not high, intensity exercise is also related to a reduction in circulating cortisol levels. More specifically, activity up to a 40% VO_{2max} can reduce cortisol since that above 60% VO_{2max} increases cortisol via enhanced secretion of ACTH [41]. As the hippocampus naturally shrinks with old age/stress, exercise is shown to reduce the rate of hippocampal volume loss, or at least, attenuate it [42]. A healthy diet pattern is important for overall stress reduction, as it is also associated with a reduced odds of depression [43]. In 2016, researchers showed that a healthy diet enriched with optional supplements (ex: Vit B3, Vit B12, folic acid, lithium, and taurine) accelerated the GABAergic activity of our bodies, which in turn negatively modulates corticoliberin (CRH), decreasing cortisol levels [44]. Taken together, the aforementioned interventions/suggestions have been linked with lower cortisol levels and thus, better stress management.

Conclusion

Medical training is one of the most stress-inducing and rigorous programs available to students worldwide. To make matters worse, the Covid-19 pandemic has had an immense influence on students who have now been transitioning into a modern era of e-learning. In this article, we discussed how stress can develop in a student's life through multiple strategies, the devastating impact of Covid-19 on our everyday health and especially on medical students, role of cortisol in memory and neuroplasticity, and lastly some interventional strategies to help students understand those factors and be able to cope with them effectively. As future caregivers, it is absolutely critical that medical students identify their particular stressors and actively engage in stress-alleviating activities so that they can enter their respective healthcare organisations with a high level of confidence and well-preparedness.

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