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AGING, STRESS, AND THE HIPPOCAMPUS

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Abstract

The hippocampus is a structure located deep inside the temporal lobe of the brain mainly responsible for learning and memory, however it is equally significant for other cognitive functions. Given the significant role of the hippocampus, extensive research has been conducted to understand how various internal and external stimuli influence it, and how this affects an individual's behavior and daily functions. In this paper, two factors will be discussed: stress, the body's natural response to challenging situations and a prevalent issue in modern times, and aging, the natural process that is highly desired to be reversible. Both of these elements play a major role, directly or indirectly, on hippocampal plasticity. In the review, a focus was put on acute and chronic stress as well as normal aging and aging encouraged by Alzheimer's disease (AD) and mild cognitive impairment (MCI).

KEYWORDS: aging, cortisol, hippocampus, norepinephrine, stress

INTRODUCTION

The hippocampal formation is comprised of different brain areas, including the dentate gyrus, hippocampus, subiculum, presubiculum, parasubiculum and entorhinal cortex.[1] Due to its crucial roles in memory and learning, the hippocampus is precisely wired in order to carry out and incorporate various information provided by afferent connections. It's better to look at the hippocampus as a singular structure as it gives us more clarity and understanding of its functions,[1] as axons in the structure provide clear indications of directionality. Perhaps the foremost role of the hippocampal formation is recording memories. As different types of memories have been defined, the hippocampus is fundamental for the production of explicit memory including episodic memory and semantic memory.[2] Episodic memory is responsible for the recollection of experienced situations and events,[3](for example, remembering when we graduated from school or passed the driving test) whereas, semantic memory stores factual knowledge that does not specifically relate to an event but rather relationships and connections between acquired facts.[4] Aging is responsible for changes in acquiring and maintaining memories, especially episodic memory (the what, when and where).[5] Depending on the time of day and the dose of released stress hormone, the effects can be interpreted as either good or bad. The following paragraphs explore different effects of stress and aging on the function of the hippocampus.

THE MECHANISMS BEHIND STRESS

Stress is a state in which an external or internal uncontrollable threat is perceived by the organism.[6] When one thinks about stress, most often they fixate on external stimuli such as stress obtained from work, familial relationships, dangerous situations, etc. What should also be considered are internal processes, and how stress occurs when the control system of the body fails.[6] Two systems are recognized and are activated in order to combat stress: the fast acting sympathetic nervous system (SNS) and the slow acting hypothalamus-pituitary-adrenal axis (HPA axis).[7] The sympathetic nervous system is responsible for the fight or flight response which is mediated by the release of catecholamines, adrenaline and noradrenaline from the medulla of the adrenal gland.[8,9] Locus coeruleus is a structure responsible for releasing norepinephrine, located in the pons of the brainstem.[10] These hormones affect many different organs of the body, including the eyes where sympathetic activation causes mydriasis and relaxation of the ciliary muscle causing far better and more focused vision.[9] Furthermore, there is an increase in heart rate, cardiac output and an increase in the release of epinephrine and norepinephrine further amplifying the fight or flight response and providing ample oxygen via blood focusing on the brain and muscles. In a study conducted by Spencer and Deak in 2021, it was examined whether SNS activation influences the relationship between age and memory practice effects.[11] The results showed that higher baseline SNS activity is linked with lower memory practice effects, irrespective of age.[11] The HPA axis explains the main mechanisms responsible for releasing stress hormones. The hypothalamus is responsible for the output of corticotropin-releasing hormone (CRH) when stimulated by direct or indirect neural input.[12] The next level of the system is the pituitary gland, found in the base of the brain. The CRH released from the hypothalamus acts to activate the release of adrenocorticotropic hormone (ACTH) from the pituitary gland.[12] ACTH is then released into the systemic circulation and after reaching the adrenal cortex it stimulates cortisol release.[12] The HPA axis can be detrimental for managing stress as the activation of it promotes the release of glucocorticoid hormones, mainly

cortisol.[13] The effector hormones of the HPA axis show predictable changes in serum levels depending on the time of day, with the maximum levels during sleep.[12] There can also be an increase because of external or internal stressors.[12] Besides the described situations, higher levels of cortisol are also found during exercise, in individuals using anxiolytic drugs and post-sexual intercourse.[12] Interestingly enough, conditions like chronic pain or anxiety do not induce increase in cortisol levels.[12] Multiple studies have shown that cortisol does not have as bad of a influence on a human body as it is perceived.[14,15] It is now known that there are characteristic daily boosts in cortisol levels which serve the purpose of being mood-protective and energizing.[16] Upon waking up, cortisol plasma levels rise thus helping us to revitalize and prepare us for the challenges of the day.[16] Similarly, the release of cortisol after stressful situations helps individuals manage emotional strain by reducing negative emotional responses.[16] Stress hormones work by attaching themselves to different types of receptors. Specifically to mineralocorticoid and glucocorticoid receptors located intracellularly. Glucocorticoid receptors are located on almost every type of cell in the body and are thus the main effector of cortisol.[12] On the other hand, mineralocorticoid receptors are expressed in very specific areas, such as most limbic areas, including the hippocampus, amygdala and prefrontal cortex.[17] Glucocorticoid receptors play a significant role in storing stress-related information for future reference while mineralocorticoid receptors have been associated with fast effects on cognitive processes such as appraisal and attention processes needed for the encoding of new stimuli.[18]

ACUTE STRESS

Acute stress protects the body by creating physiological changes that help overcome hazards.[19] In addition to helping an organism fight stress, glucocorticoids and adrenaline also improve some processes of learning and memory formation.[20] Undoubtedly, information encoded into memory during stressful encounters remains very well remembered.[10] Changes that happen in the brain while experiencing acute stress are mediated by norepinephrine released from the locus ceruleus.[10] The activity that arises from norepinephrine release supports neural plasticity that facilitates memory formation.[10] Current studies consistently show that a mild increase in the levels of stress hormones plays a positive role in memory functions.[21] Extensive research has been conducted to understand the morphological changes in the hippocampus following acute stress, revealing a reduction in spine density. In 2010, Chen et al. conducted research on mice in an effort to understand how acute stress affects the hippocampus.[22] The results showed that acute stress reduces the density of dendritic spines mainly in the CA3 area which could explain the decline in learning and memory following acute stress.[22] The loss in memory and learning was correlated with the reduction in the spine density of the CA3 area. Furthermore, the researchers then administered a CRH receptor type 1 blocker to the animals, showing that by preventing CRH from binding to its receptor they could halt the memory and learning impairment by stopping the reduction in spine density.[22] This research has revealed the complex nature of different elements affecting the same target. In contrast to these results, in research investigating long-term stress responses, a reduction in dendritic arbors was identified.[22–28] In 1997, Morandi-Raikova and Mayer conducted research on young chicks. Although avians and mammals are two different taxonomic groups , the hippocampus is highly comparable.[29] In the study, corticosterone (the equivalent of cortisol in animals) was used to test its ability to facilitate memory formation.[30] The results showed that elevated corticosterone levels following a difficult task facilitated the formation of short-term memory (lasting less than 9 hours).[30] This effect was dosage-dependent, such that when 1mg of corticosterone was administered right after training, retention was improved, but anything above 1mg had the opposite effect on memory retention.[30] A different study by Yuen et al. showed that the relationship between stress and cognitive function shows an" inverted U" relation, meaning that moderate levels of stress hormones positively influence cognitive function while too high or too low levels of glucocorticoids exhibit a decline in cognitive function.[21]

THE HIPPOCAMPAL FORMATION

The hippocampal formation is a structure composed of different regions connected by intracortical connections. The regions that complete the hippocampal formation are the entorhinal cortex, the dentate gyrus, the hippocampus proper[31](consisting of CA3, CA2 and CA1 regions), the subiculum, the presubiculum and the parasubiculum.[32] Together they complete a cortical structure responsible for encoding and storing memories, spatial information and episodic events.[33] Moreover, the hippocampus is related to other cortical structures in its vicinity by extrinsic connections, making it an integral factor of higher functions such as emotional responses.[34] What makes this structure unique is the ability to receive multimodal sensory information from other parts of the brain and understand them using their own inner neuronal network.[1] The hippocampal formation is internally connected by cell projections from one region to another, thus creating different pathways. The trisynaptic circuit is the main pathway of transducing sensory information from the superficial layers of the entorhinal cortex to deeper layers of subsequent regions.[35] Information flows from layer II of the entorhinal cortex[35] to the dentate gyrus by the perforant path.[36] The dentate gyrus extends its projections, called the mossy fibers to the CA3 region, and the CA3 region by the so-called Schaffer collaterals gives neuronal projections to the CA1 region.[35] The trisynaptic loop is closed when CA1 neurons carry information to layer V of the entorhinal cortex.[35] This circuitry highlights the entorhinal cortex as the major input and output station of the hippocampal formation and a focal point in the cortico-hippocampal circuit.[37] Furthermore, the entorhinal cortex transmits both spatial and non-spatial sensory information.[33] Axons from the CA1 region and the subiculum project to the alveus, fimbria and the fornix, creating an output pathway from the hippocampus.[37] Because of that, CA1 is considered the major output from the hippocampus as it sends projections to surrounding structures: subiculum, prefrontal cortex and the amygdala.[33] Lesions in the CA1 region lead to serious memory damage.[33,38] CA3 is part of a circuit crucial for encoding episodic memories.[39] The mossy fiber pathway that projects to CA3 acts as a "high-pass filter"

that translates cortical signals into the hippocampal code fundamental for memory construction.[39] To conclude, CA3, through its collateral connections, acts as the major area responsible for facilitating "fast associations between any spatial location and an object or reward".[39] The architecture of the area permits it to make relations between time, objects and rewards required for episodic memory.[39]

CHRONIC STRESS

Chronic stress is a threat to the body's homeostasis. As already mentioned, stress hormones are beneficial to a certain degree, but when a person is dealing with long-term stress, their defense mechanisms are weakened and some organs start experiencing damage, including the hippocampus itself. CA3 is a complex part of the hippocampus with great responsibility in memory processes.[40] It is characterized by rich internal connectivity, which is larger than any other hippocampal area.[40] But what happens when long term stress acts on the area that is exceedingly sensitive to stress, namely area CA3? Research shows that prolonged exposure to stress slightly reduces the volume of the CA3 area, but does not reduce the total number of neural cells.[39] Alongside the decrease in volume, there is also a reduction in apical dendritic complexity and length of pyramidal neurons in CA3.[39] When exposed to prolonged release of stress hormones, there was also a significant loss of mossy fiber synapses recorded.[39] A damaged hippocampus is not only lacking in memory formation, but it also promotes the expression of psychopathologies in genetically predisposed individual.[39] A loss of around 15% of total hippocampal volume was discovered in individuals with depression.[39] Alongside the reduction in volume, a noticeable decrease was seen in neurogenesis and dendritic stability.[39] Antidepressant medications can actually reverse the damage made by depression by stimulating adult neurogenesis.[39] Chronic stress is not just a cumulative effect of many acute stress periods.[39] If that was the case, chronic stress would enforce a permanent condition of what is typically seen hours after acute stress.[39] The defining feature of chronic stress that separates it from acute stress is that the repercussions of chronic stress are far more complex and extensive.[39] In 2007, research was conducted by McLaughlin et al. on rats in an effort to evaluate the effects of chronic stress on hippocampal morphology. Different groups of rats were subjected to differing durations of stressful events: 2h of stress for 10 days (10d), 2h/21d, 6h/10d, and 6h/21d.[41] The scientists discovered that the 6h/21d group showed the biggest difference in hippocampal morphology.[41] Rats in the mentioned group displayed withdrawal of apical dendrites in the CA3 area, characterized by a reduction in apical branch points and apical branch length.[41] These results correlate with impaired spatial memory in the rats.[41] The reasoning behind conducting such research and focusing on changes in the CA3 region is due to familiarity with the fact that, "stress-induced reductions in dendritic arbors are expressed within the CA3 region first before other hippocampal areas show changes".[41]

AGING

Relating aging effects on the hippocampus is difficult in healthy individuals. Partly because there is a lack of quality research on it, the research that has been done gives contrasting results, and also because the noticed changes correlate only to a loss of hippocampal volume.[42] What is interesting is that the absolute cortical volume slowly starts to decrease from 20 years of age, but the hippocampus holds a steady volume until about 60 years old.[43] The latest research shows that the hippocampus also plays a role in processing the perception of speed, intelligence and executive function, and all of these functions decline in the context of cognitive aging in healthy individuals.[42] It's worth noting that not all hippocampal functions start deteriorating with decreased hippocampal volume. Those functions are implicit learning and semantic memory.[44,45] To separate changes that happen due to normal aging and to distinguish them from a pathological finding, normal cognitive defects in elderly are as follows (>60 years of age): reduction in mental speed, executive function and episodic memory.[43,47–50] Episodic memory normally starts to worsen from the age of 50-60.[43] In 1998, a project was started by Fjell et al. which lasted for more than 25 years as they were trying to find out how memory functions change during adult life and aging, and to determine the risk factors for dementia. 1500 individuals participated to help the researchers create three groups in terms of memory change.[43] The groups were named: maintainers, age-typical decliners and decliners.[43] It was revealed that being physically active or living with someone maintained memory functions.[43] The effect was enhanced for female participants of the study.[43] On the other hand, predictors of a decline in memory functions were a lower level of achieved education, male sex, living alone, while the strongest predictor was advanced age.[43] Considering limited research concerning the impact of age in healthy individuals on the hippocampus, more conditions such as Alzheimer's disease (AD), mild cognitive impairment (MCI) and other dementias will be highlighted. As much as a decrease in hippocampal volume is natural in elderly people, those with conditions listed above show a bigger drop in volume than their unimpaired peers.[42] Hippocampal decline in individuals with MCI is a predictor for the development of AD in the future. That relationship could be significant in screening individuals with an increased risk of developing AD and or other dementias. In 2010, a study was conducted by Mueller et al. to find atrophy patterns in the hippocampus in individuals with MCI and AD.[51] The research presented two leading findings: in the AD group, the most pronounced loss of volume was found in the transition between CA1 and CA2, the CA1, and the subiculum, while in the MCI group low-volume areas included only the transition between CA1 and CA2.[51] In both the MCI and the AD group, volume was unchanged in the CA3 and the dentate gyrus.[51] This is in contrast with normal aging, as this group showed a loss of neurons and total volume only in the CA1 area.[51]

CONCLUSION

Ample research has been done to determine the extent of effects of both short and long-term release of stress hormones on the body, but more importantly for this review, the hippocampus. It is important to distinguish between positive and negative results of stress hormones on the whole body and emphasize that in many instances stress hormones cause protective responses. While acute high levels of stress hormones facilitate memory formation, the time frame following an acutely stressful situation shows a decline in the formation of memories and learning. The effects of stress hormones are also dose dependent, with levels too low and too high displaying cognitive impairment. It's important to note that acute stress and prolonged exposure to stress show different effects on the hippocampus. Both acute and chronic stress affect the morphology of the hippocampus, with the acutely high levels of stress hormones reducing the density of dendritic spines in the CA3 area leading to decreased learning and memory forming ability. On the other hand, chronically elevated levels of stress hormones display more complex changes in the morphology of the hippocampus, leading to impaired memory formation and an increased risk of developing psychopathologies. While contrasting results are sometimes seen, there is no debate that chronic release of stress hormones has a negative impact on individual's behavior and cognitive functions. Age is the greatest factor influencing the decline of memory formation. Physiological aging affects the ability of the hippocampus to create episodic memories and impairs executive functions. While there is no remedy to prevent aging of the hippocampus, creating healthier habits and surrounding ourselves with people, could maintain hippocampal functions for longer.

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STARENJE, STRES I HIPOKAMPUS

Sažetak

Hipokampus je struktura smještena duboko u temporalnom režnju mozga te je odgovorna za učenje i memoriju, ali je jednako važna i za ostale kognitivne funkcije. Budući da je struktura od velikog značaja, mnogo je istraživanja učinjeno kako bi se odredilo kako različiti unutarnji i vanjski čimbenici utječu na hipokampus i posljedično na uloge u čovjekovom ponašanju i svakodnevnim funkcijama. Ovdje će se raspravljati o dva faktora. Stres, prirodni odgovor tijela na izazovne situacije te prevladavajući izazov u modernom vremenu i starenje, prirodni proces za koji je željno da bude reverzibilan. Oba elementa imaju veliku ulogu, izravno ili neizravno na plastičnost hipokampusa. U ovom radu će fokus biti na akutnom i kroničnom stresu kao i na normalnom starenju i starenju potaknutom od strane Alzheimerove bolesti i blagog kognitivnog poremećaja.

KLJUČNE RIJEČI: Hipokampus, kortizol, noradrenalin, starenje, stres