The Effect of Long-term Stress on Hippocampus and the Involvement in the Pathophysiology of Psychological Disorders, Suicide, and Alcohol Use Disorder

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Stress is defined as the “relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering wellbeing” (Folkman, Lazarus, Gruen, & DeLongis, 1986, p.2). When a stressor is experienced, our body activates a stress response mainly through the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS). As this paper focuses on long-term stress, the focus would be on the hypo-hyper activity of the HPA axis as it stimulates the adrenal cortex, not the adrenal medulla which mediates short-term stress response that affects ANS. When the HPA axis is activated, either a hyper-or-hypo response occurs that disturbs the body’s homeostasis. However, as soon as the stressor finishes, the process of negative feedback begins to terminate the stress response and the HPA axis activity reaches normal again (Mcewen, 2007).

The HPA axis is activated when any stressful stimuli cause the hypothalamus to stimulate the anterior pituitary gland that releases the adrenocorticotropic hormone (ACTH). ACTH further stimulates the adrenal cortex that releases cortisol, a primary glucocorticoid stress hormone (Learning Lumen). A glucocorticoid hormone is any type of steroid hormone produced by the adrenal cortex that is involved in metabolism and has anti-inflammatory properties. Cortisol specifically is involved in the regulation of emotion, cognition, reward,
immune functioning, and energy utilization (Adinoff, Ruether, Krebaum, Iranmanesh, & Williams, 2003).

A short-term, acute stress response from the body is beneficial to humans as it enables us to effectively cope with stress (Smith & Vale, 2006). For example, fear is a sense of an immediate threat and a stress response such as the fight or flight response can be beneficial for survival. Moreover, acute stress can be eustress as it has motivational properties for some individuals e.g. when a deadline for an assignment is approaching. However, a long-term, chronic stress response is distress as it persistently dysregulates homeostatic regulation and is also detrimental to mental health.

Therefore, the length of time an individual experiences stress is an important variable. In the case of behavioral problems such as aggression and attention problems, cortisol levels are abnormally high when the behavioral problems begin but, reach an abnormally low level when stress continues for an extended period of time. The abnormally low cortisol levels are based on the body’s adaption to long-term stress which paves the way for a blunted affect. (Ruttle et al., 2011).

In addition, to the length of time, a sustained hyper or hypoactivity of the HPA axis results in abnormally high or low levels of glucocorticoids which can be detrimental to human health. For example, due to the hypersecretion of glucocorticoids, an individual begins to develop Cushing’s disease characterized by excessive glucose in blood and accumulation of fat around the face and neck (Learning Lumen). With persistent hyperactivity of the HPA axis, the levels of glucocorticoids continue to remain elevated from normal levels. Therefore, as cortisol levels remain elevated, so do the glucose levels because, cortisol increases the metabolism of glucose in order, to provide adequate energy to cope with stress (Khani & Tayek, 2001)
Moreover, cortisol levels can not only fluctuate due to stress but also, due to the circadian rhythm (Dickmeis, 2008). Cortisol levels peak in the early morning and drop to the lowest levels at night, but the cortisol peak varies according to the individual’s normal wake-up time. Furthermore, cortisol levels do not correlate with age, gender, body composition, and growth rate (Knutsson et al., 1997).

**Glucocorticoids and Brain Damage**

The hippocampus, a limbic system structure plays a fundamental role in learning and memory. However, it is susceptible to damage by a sustained increase in glucocorticoid levels because the hippocampus has the highest number of receptor sites for glucocorticoids (Sapolsky, Krey & Mcewen, 1984). Recall glucocorticoids such as cortisol are released during a stress response. The increased glucocorticoid level damages the hippocampus by dendritic retraction, which is a reversible form of plasticity that results in dendritic reconstruction without irreversible cell death. Although the hippocampus can recover from dendritic retraction without a major cell loss, it remains vulnerable to neurotoxicity and metabolic challenges during the time when levels of glucocorticoids remain elevated. Moreover, the duration of dendritic retraction can last from weeks, months, to years (Conrad, Magariños, Ledoux & Mcewen, 1999).

As mentioned above, a stress response is terminated through negative feedback and the hippocampus receptor sites are susceptible to damage by elevated glucocorticoid levels. As the hippocampus is responsible for providing negative feedback, Sapolsky et al. (1984) research investigated if there was an impact of damaged hippocampus glucocorticoid receptor sites on the levels of cortisol. The research findings supported that when the hippocampus receptor sites for glucocorticoids were damaged in rats, the levels of cortisol remained elevated because negative feedback was not provided by the hippocampus to terminate the
stress response. Hence, chronic stress stimulates elevated levels of glucocorticoids that result in the impairment of hippocampal functioning which further contributes to the dysregulation of the HPA axis (Sapolsky et al., 1984).

**Neurotoxicity and Metabolic Challenge**

Neurotoxins cause damage to the brain or peripheral nervous system by exposure to natural or man-made toxic substances e.g., lead and ethanol. The hippocampus is susceptible to neurotoxin damage only when there is a history of chronic stress. This is because during chronic stress the dendritic retraction lasts for at least 4 days which is a larger window than for acute stress (Conrad, 2008). During acute stress, glucocorticoid levels reach baseline within hours and thus, do not impair the hippocampal and the HPA axis functioning. Thus, a history of chronic stress is critical for hippocampal susceptibility to neurotoxins as the window for the process of dendritic retraction increases. This remains true even when acute stress lasts for up to two weeks (McLaughlin, Gomez, Baran & Conrad, 2007).

A metabolic challenge includes restricted blood flow, low sugar, etc. Individuals with chronic stress are vulnerable to an extended period of hippocampal plasticity. As a result, the longer the period, the greater the likelihood of an occurrence of a metabolic event. The end result can be a permanent hippocampal cell loss and/or an inability to recover from the change in the hippocampus volume. As we will later discuss, antidepressant or anti-glucocorticoid treatment is very helpful in the recovery of the hippocampal volume in depression and/or PTSD. Therefore, sometimes the damage is not permanent but, the possibility of permanent damage remains present that persists despite anti-depressant or anti-glucocorticoid treatment (Conrad et al., 1999).

**Affective Disorders**
The dysregulated hypothalamic-pituitary-adrenal (HPA) axis is associated with preceding the development of an affective disorder, and we would explore how this dysregulation correlates with hippocampal damage.

Depression

A widely supported phenomenon is that a stressful event not only contributes to the development of depression but also, in the maintenance of depressive symptoms over time. During a study, adolescents with depression and healthy controls were exposed to psychosocial stress to record their cortisol levels, where both groups showed an increase in cortisol levels after exposure to a stressful event. However, adolescents with depression displayed a continued rise in cortisol levels while cortisol levels for healthy controls reached the baseline level within an hour (Rao, Hammen, Ortiz, Chen & Poland, 2008).

Elevated cortisol levels have been associated with a reduced hippocampal volume (Wiedenmayer et al., 2006) and hippocampal volume is negatively correlated with depressive symptom severity (Bremner et al., 2000). The change in hippocampal volume explains why ECT is a fast-acting treatment for depression. Nordanskog et al. (2014) observed an increase in the hippocampal volume immediately after bilateral ECT however, the increase was not permanent, and the hippocampus returned to its original volume within 6 months.

Therefore, a small hippocampal volume and dysregulated HPA axis with elevated cortisol levels are major biological determinants of depression.

Bipolar Disorder

We have seen that the HPA axis is dysregulated in depression but, it also remains dysregulated in individuals with bipolar disorder. The HPA axis continues to be compromised in the offspring of parents with an affective disorder. Ellenbogen, Santo, Linnen, Walker, and Hodgins’s (2010) longitudinal study concludes that the offspring of parents with bipolar had
increased daytime cortisol level that continued through late adolescence and young adulthood. Another study investigated the stability of salivary cortisol and found it to be fairly stable over repeated sampling across a year among high-risk individuals (offspring of individuals with bipolar) and healthy control individuals. The study measured cortisol levels upon awakening, daytime, and evening because of cortisol diurnal rhythm. The research found that salivary cortisol remained stable throughout early adulthood among high-risk offspring. However, the yearly samples showed an exception for evening cortisol samples, where healthy controls had higher cortisol levels than high-risk individuals (Goodday, Horrocks, Keown-Stoneman, Grof & Duffy, 2016). Therefore, the subtle changes over time in the HPA functioning could be associated with increased vulnerability for the development of an affective disorder.

Another important finding is that the late-onset (equal or greater than 30 years) of bipolar disorder is associated with life events and thus, perpetuated by stress. This was supported by the research finding where hair cortisol levels were higher in individuals with late-onset than in early-onset or healthy controls, where early-onset is linked to genetic vulnerability (Manenschijn et al., 2012).

**Eating Behavior**

Stress has been found to be a stimulant that induces overeating which results in weight gain. To become more specific, one of the studies focused on the type of food that is eaten during stress. Dallman et al. (2003) found that chronic stress induces either an increase in comfort food intake or a decrease in food intake. The food intake was directly proportional to bodyweight so, if during a stressful period there was an increase in comfort food intake, the researchers found a gain in body weight as well. The researchers also concluded that
overeating of comfort food stimulates cortisol in response to stress that results in abdominal obesity (Dallman et al., 2003).

Nevertheless, it is unclear if overeating is synonymous with binge-eating. However, if binge-eating is synonymous with overeating, associations can be established to find the answer to why individuals with bulimia have high comorbidity with depression (Patel, Olten, Patel, Shah & Mansuri, 2018). When an individual suffers from chronic stress, the levels of cortisol remain elevated which results in overeating (binge-eating) of comfort food. Quite possibly, the comfort food could be high in sugar and fat, posing a threat of a metabolic challenge and thus, making the hippocampus vulnerable to damage during dendritic retraction. During that time, changes in the hippocampal volume can also occur, which could decrease the hippocampal volume, recall a smaller hippocampal volume correlates with depression. Therefore, individuals with bulimia binge-eat comfort food that poses a threat of a metabolic challenge that results in lower hippocampal volume, resulting in an on-set for depression. The assumption that comfort food could be high in sugar and fat, was supported when the experimental group underwent laboratory-induced stress and ate sweeter, high-fat foods than the control group, that did not undergo laboratory-induced stress (Oliver, Wardle & Gibson, 2000).

Most of the metabolic challenges can be linked to obesity. In order, to find if the type of diet had any subsequent effects on stress-induced hippocampal dendritic retraction, a study on rats was performed. The study found that a high-fat diet exacerbated stress-induced hippocampal dendritic retraction (Baran et al., 2005). Therefore, individuals can reduce the risk of hippocampal vulnerability during times of stress through a fat reduction in their diet.

Post-traumatic Stress Disorder
A small hippocampal volume and HPA axis dysregulation are also widely observed in individuals with PTSD (Bremner et al., 1995). The presence of a traumatic event onsets chronic stress and as we have seen, chronic stress causes changes in the hippocampal volume (Gurvits et al., 1996). A study focused on Vietnam Veterans found that a smaller hippocampal volume correlated with longer combat exposure. Hence, the longer the combat experience, the longer the maintenance of elevated cortisol levels and thus, the probability of hippocampal volume change and the duration of dendritic retraction increases. This trend was visible in individuals without combat stress as well. Patients with PTSD who were exposed to childhood sexual abuse or other trauma also displayed a smaller hippocampal volume which like depression, correlated with symptom severity (Stein, Koverola, Hanna, Torchia & McClarty, 1997; Villarreal et al., 2002). Antidepressant treatment was shown to increase the hippocampal volume and thus, the symptoms of PTSD alleviated (Vermetten, Vythilingam, Southwick, Charney & Bremner, 2003).

**Alcohol Use Disorder**

There has been a strong association between traumatic events, and the escalation of alcohol use (Hasin, Keyes, Hatzenbuehler, Aharonovich & Alderson, 2007). Veterans who are shown to develop PTSD were also at a higher risk of developing alcohol use disorder (The Soldier's Heart). However, both alcohol consumption and withdrawal results in the elevation of glucocorticoid levels and attributes to HPA dysregulation. As a result, the sustained increase in glucocorticoids makes the brain susceptible to damage (Rose, Shaw, Prendergast & Little, 2010). The brain structure mentioned recurringly in this paper, the hippocampus also becomes vulnerable and this answers why even after treatment, some individuals continue to suffer from cognitive deficits (Rose et al., 2010; Staples & Mandyam, 2016).

**Suicide**
For most of the disorders discussed in this paper, there has been a trend of higher cortisol levels, however, individuals vulnerable to suicide have lower cortisol levels, especially upon awakening in the morning. Hence, lower cortisol levels predict suicidal ideation. A stressful event, such as childhood trauma has been identified as an important determinant of lower cortisol levels upon awakening and higher suicide risk during adulthood. The childhood trauma is associated with a dysregulated HPA axis due to chronic stress, which results in lower levels of cortisol during a stress response. A study found a significant association between childhood trauma and low cortisol levels upon awakening, which predicted higher suicidal ideation over the course of at least one month (O'Connor et al., 2020).

There is no direct association between the changes in the hippocampus that are linked with chronic stress that directly account for suicide. However, individuals with depression have a lower hippocampal volume that can be associated with dysregulated HPA axis so, an already lower hippocampal volume due to depression can be accounted for suicide. Around 15% of individuals who suffer from depression commit suicide (Nock, Hwang, Sampson & Kessler, 2009) and the suicide rate increases if co-morbid disorders are present e.g. depression and anxiety (Gonda, Fountoulakis, Kaprinis & Rihmer, 2007). Furthermore, depressed suicide attempters have been observed to have a smaller hippocampus than depressed patients without suicide attempts. The significant difference was not associated with past attempts or since the first suicide attempt rather to the acute suicide attempts, suggesting that a smaller hippocampal volume continues to be present in individuals with depression during active suicidal ideation (Colle et al., 2015).

Conclusion
Most disorders follow the Diathesis-Stress Model where the trajectory begins with a predisposition vulnerability (early-onset bipolar) or no predisposition (late-onset bipolar). However, the symptoms begin to precipitate once a major stressor is experienced with or without a predisposition and the effects of chronic stress, in particular, perpetuate the symptoms. As we have explored in this paper, chronic stress makes the hippocampus vulnerable to damage and the reason why the hippocampus is so susceptible is that it has the most receptor sites for glucocorticoids e.g., cortisol. The hippocampal damage e.g., the changes in volume further perpetuate the symptoms of a disorder. Moreover, cortisol levels can serve as a biomarker to predict the development of various disorders. For example, we have seen lower cortisol levels upon awakening were a distinctive feature of active suicidal ideation.

Indeed, stress plays a significant role in mental health but amidst today’s stressful climate, stress is hard to dodge. Nevertheless, to nurture our mental health we should try to minimize stress the best we can.
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