The Effects of Early Adverse Life Experiences on the HPA Axis and Their Impact on the Development of Depression

Katherine Copeland and Claire Gorey

University of Kansas

Abstract

In this review, the effects of early life stress (ELS) on the hypothalamic-pituitary-adrenal (HPA) axis and their role in the development of Major Depressive Disorder (MDD) later on in life are discussed. The HPA axis mediates one of the major stress response systems in the human body, and therefore, the damaging effects of ELS play a major role in the development of MDD. By examining research that studied non-depressed abused children, depressed adults, non-depressed abused adults, and control subjects, neurobiological similarities and differences are revealed. The hyperactive responses to ELS in childhood appeared to have adapted to chronic stress, and consequently, these individuals exhibit blunted responses later on in life. These blunted responses mimic those of depressed individuals without ELS, and thus, these responses may represent a vulnerability to developing depression. Despite this similarity, the hyperactive HPA axis in childhood results in a number of neurobiological differences between abused depressed and non-abused depressed individuals. Pending further research in this area, specific treatments for people with MDD and ELS would be supported.

Introduction

Researchers have classified early life stressors (ELS) as moderate to severe adversities experienced before puberty. Some of the common early life stressors identified are sexual, physical, and emotional maltreatment, but ELS also includes life stressors such as chronic illnesses, accidents, natural disasters, wars, poverty, parental loss, unstable families, and dysfunctional parent-child relationships (Heim, Plotsky, & Nemeroff 2004). It has been reported that there are about 1.5 million instances of early adverse life experiences each year in the United States, and almost half of these events were more serious in nature than others previously listed (e.g., physical, sexual, or emotional abuse) (Heim & Nemeroff 2001). It is essential to determine the effects of early adverse life events because this knowledge will aid in the development of successful treatments and interventions. This literature review will give an overview of the hypothalamic-pituitary-adrenal (HPA) axis and the studies examining the effects of childhood maltreatment on the HPA axis. It will also discuss how genes, gender, and the environment mediate the effects of ELS and will propose a working model for why depression develops after ELS for some individuals but not for others. Then, it will discuss possible treatment specific options for those with a trauma history. Lastly, it will help advance the existent research by discussing additional studies that could examine this phenomenon from a developmental perspective. The expected, differential effects could provide supporting evidence for treating those with ELS and MDD differently than those with just MDD.

Evolutionary and Developmental Impacts on the HPA Axis

The HPA axis mediates one of the major stress response systems in the human body. The function of the HPA axis has not changed much since we lived in caves, despite changes to our social environment. Activation of the HPA axis is referred to as the "defeat reaction" or the helpless reaction to stress because it is often triggered by stressors that appear to be out of the person's control (Bauer, Quas, & Boyce, 2002). The HPA response was shaped by evolutionary forces that helped our ancestors survive life-threatening situations such as extreme cold, drought, famine, and threats to social dominance. However, in modern society, these same systems are activated much more frequently and by very different types of events, which are usually not life-threatening. Although this is the case with many types of stressors that we encounter today, it is not necessarily the case for children who are abused by their parents. Child maltreatment can potentially be life-threatening, and it is certainly a case in which children are helpless to get themselves out of the situation. If the abuse happens to be chronic, children's HPA Axis' will be in a constant state of activation. This enhanced activity will create sustained, chronic levels of cortisol throughout crucial stages of childhood development (Heim et al., 2002). The body will eventually adapt to these high levels of cortisol and continue to produce them even after the stressors have been resolved. When this occurs, it is much harder for the body to respond appropriately to novel stressors that are presented later on. In many cases, a hyperactive HPA axis produced by child maltreatment would lead to an adult with a blunted stress response, resembling the neurobiological activity of those with MDD. This eventual overlap in symptoms suggests a link between childhood maltreatment and the development of MDD later on in life. However,

despite this overlap, the effects of sustained CRH and cortisol during the critical periods of child development induces neurobiological changes that differentiate those with ELS and MDD from those with just MDD (Heim et al., 2002).

In a healthy individual, the HPA axis activation starts after it has received information from the amygdala and hippocampus. The amygdala sends information when the individual is experiencing emotions such as fear or stress-induced anxiety, and the hippocampus sends it when the individual is recalling a past memory. The HPA axis responds to the input from the amygdala and hippocampus by stimulating the corticotropin-releasing factor (CRH) in the hypothalamus. The CRH then stimulates the secretion of the adrenocorticotropic hormone (ACTH) in the anterior pituitary, leading to increased concentrations of cortisol produced by the adrenal cortex. Once the stressor has been resolved, a negative feedback loop suppresses the release of CRH and ACTH in order to regulate the concentration of cortisol being released into the body. Cortisol brings the body back into homeostasis and deactivates the stress response (Chrousos & Gold 2010, Shea, Walsh, MacMian, & Steiner, 2004). However, chronic early life stress damages the HPA axis, and as a result, the normal responses to stress are dysregulated. When the stress response is dysregulated, the HPA axis becomes hypersensitive. The dysregulated HPA axis will be activated frequently and for longer durations. The hyperactivity of the HPA axis will result in an increased amount of cortisol being released, and thus, more cortisol will be exposed to areas in the body, especially in the brain. This can have detrimental effects, not only on the normal functioning of the HPA axis, but also on children's development (Joels, 2010). The effects of ELS on the HPA axis in children will be examined in the following paragraphs (Liu et al., 1997; Kaufman et al., 1997). Then, adults with a history of ELS will be observed to discover how the HPA axis adapts to stress in adulthood, how it differs from childhood, and how it is different from those with current MDD but no history of ELS (Shenk, Noll, Putnam, & Trickett, 2010; Heim et al., 2002). These neurobiological differences in the HPA axis, along with further evidence addressing the gaps in the research and examining effective treatment options for those with ELS and MDD, will provide empirical support for the development of specialized treatments for those with ELS and MDD.

The HPA Axis' Adaptive Response in Childhood Compared to Adulthood

The HPA axis responds differently in children with ELS than it does in adults with ELS. In order to observe these differences, researchers studied the effects of early life stress on the stress response system in non-human animals first to determine what kind of responses to expect in humans. One study revealed that environmental events during the first ten days of a rat's life play a role in shaping the stress response of the HPA axis (Liu et al. 1997). They discovered that the HPA axis response to stress was less active if the mother rat exhibited a greater frequency of licking and grooming their offspring during infancy. Specifically, those offspring displayed lower ACTH and corticotropin responses to stress (Liu et al, 1997). The results of these studies show that social relationships appear to be important to development in non-human species, and the findings can be generalized to human species as well.

In the absence of a positive support system, humans who experience abuse and ongoing stressors exhibit significant dysregulation of the HPA axis system (Kaufman et al. 1997). For instance, depressed abused children who would be likely to lack a positive support system appear to produce a stronger hormonal stress response. In one study, 39 children between the ages of 7

and 13 were given doses of CRH intravenously in order to trigger the HPA stress response. Depressed abused children exhibited a greater increase in ACTH and cortisol when compared to depressed non-abused children or the control group (Kaufman et al, 1997). Combined with the evidence from Liu et al. (1997), it appears that the initial hormonal trigger of the HPA axis produced elevated levels of CRH, ACTH, and cortisol in children who experienced ELS.

Although Kaufman et al. (1997) and Liu et al. (1997) showed elevated CRH, ACTH, and cortisol levels in response to stress in children, adults with a history of ELS and current MDD exhibit different neurobiological effects to stressors. One study compared four groups after the administration of the CRH intravenously, and it was found that women with a history of ELS and current MDD show a blunted, or decreased, ACTH response to the CRH challenge (Heim et al. 2001). These results were observed again in a study of 144 women, which measured their cortisol levels before and after the presentation of a laboratory stressor (Shenk et al. 2010). Therefore, it may be that the body adapts to repeated stress by forming a blunted ACTH response to protect itself and to prevent harm to the body.

When evaluating these four studies, the effects of ELS are different when observing children with ELS and adults with ELS and MDD. Children with current ELS exhibit augmented ACTH in response to CRH stimulation (Kaufman et al. 1997). Consistent with human data, rats that were handled during the first ten days of life displayed higher ACTH and corticotropin responses to stress than ones that were not (Liu et al., 1997). Therefore, it appears that children with a history of ELS exhibit elevated CRH, ACTH, and cortisol in response to stress. However, adults with MDD show a blunted or lower stress response, not an exacerbated one. Exposure to CRH produces a blunted ACTH and cortisol response that mimics the HPA axis activity of individuals with MDD without ELS (Shenk et al., 2010; Heim et al., 2001). Therefore, it is hypothesized that the initial hyperactivity of the HPA axis evolves into a blunted response over time because of the down-regulation of pituitary CRH receptors as a consequence of hypothalamic hypersecretion. It is possible that this results in symptoms of depression because excess CRH is released in the extra-hypothalamic circuits (Heim et al., 2002).

Thus, it is proposed that ELS produces a vulnerable phenotype, and upon further exposure to stress in adulthood, individuals with ELS are more susceptible to developing MDD. Those with a history of ELS and current MDD and those with current MDD alone may display similar neurological effects such as a blunted ACTH response to CRH administration and elevated levels of CRH in extra-hypothalamic circuits. However, despite the overlap, there are marked differences between the two groups of individuals.

Neurobiological Differences Between MDD with ELS and MDD Alone

Although individuals with current MDD and ELS have similar neurobiological responses to stress as individuals with MDD alone, there are other neurobiological differences that exist between the two groups. These differences are observed when the hippocampus, CRH 1 pathways, and oxytocin levels are examined in the two clinical groups. For instance, those with a history of ELS exhibit decreased hippocampal volume (Joels, 2010). The left hippocampus in those with a history of ELS is 18% smaller than those with MDD alone. This may be a result of cortisol hypersecretion during development and over the course of time. Cortisol has been shown to result in neurogenesis and, as a result, restricts the development of new cells, the migration of cells, and the differentiation of neurons (Joels, 2010). Therefore, since the hippocampus is still

developing when early life stress occurs, the hypersecretion of cortisol will not allow the hippocampus to function and develop normally. As a result, these individuals' stress response systems would be even more dysregulated because the hippocampus plays such a pivotal role in the negative feedback loop. They would also have a harder time with memory and concentration because the hippocampus would have trouble converting short-term memories into long-term memories (Vythilingham, 2002). This decreased concentration and memory mimic some of the behavioral symptoms of major depression.

The hippocampal atrophy existent in those with a history of ELS reveals one of the neurobiological differences between those with ELS and MDD and those with MDD alone. However, there are also differences in the CRH 1 pathways and oxytocin levels. Those with a history of ELS show an even greater dysfunction in their CRH 1 pathways than those with MDD. Evidence of this greater dysfunction is proven through the increased levels of CRH in the cerebrospinal fluid of individuals with a history of ELS compared to those with just current MDD (Kehne and Maynard, 2008). Although those with ELS had higher CRH in the cerebrospinal fluid, they showed decreased concentration of the neuropeptide oxytocin compared to those with MDD alone. Oxytocin has a role in mediating social affiliation, parent and child attachment, social support, trust, and also protects the stress response. In a famous study comparing nursery-reared monkeys to mother-reared monkeys, nursery-reared monkeys displayed markedly decreased oxytocin levels, and as a result, demonstrated decreased reciprocal social behaviors and decreased likelihood to use social support to mediate their response to stress (Winslow et al., 2003). Early life stress disrupts the development of brain components involved in social attachment. Those with ELS, then, are more vulnerable to the development of depression.

The overlap in neurobiological responses in those with current MDD and those with current MDD and ELS represent the effects of depression. However, the neurobiological differences suggest that the effects of ELS may require additional or alternative treatments than those recommended for patients with MDD alone. Early life stress produces persistent changes in the HPA axis and related systems during development, and as a result, these systems function differently than in those who experience stressors in adulthood and develop MDD.

Factors that Moderate the Effects of ELS

Through the analysis of ACTH levels, cortisol levels, and the HPA axis, researchers have demonstrated the impact of early adverse life experiences and have shown a link between childhood trauma and the development of major depression later on in life. However, some individuals who experience early adverse life experiences do not develop major depression. It is crucial to identify variables that moderate the effects of childhood trauma on the development of major depression. The characteristics of the early life stress, such as the timing and frequency, are among these variables. However, genetics and the environment also play a major role on whether or not an individual will develop depression.

Frequency and Timing of Early Life Stress

Even the characteristics of the early life stress can influence the developmental outcome. Some of these characteristics include the frequency of the stressor and the timing of the stressor. When studying the effects of the frequency of ELS on mental health, one study revealed a

dose-response relationship between the number of early life stressors and the number of depressive symptoms (Feletti, et al., 2003). When examining rat pups under stress during different time periods in early development, researchers have seen differential outcomes, i.e. significantly different cortisol and ACTH levels (Enthoven et al., 2008). This evidence suggests that even the characteristics of the early life stress can have differential effects on an individual. However, because most of the research on this topic is on animals, further studies with humans will be necessary to substantiate the results found in the studies discussed.

Gene by Environmental Interactions

Although the different characteristics of the early life stress influence the development of major depression, genes also interact with early life stress to produce varying outcomes. For those with a history of early adverse life experiences, multiple studies indicate that the importance of the 5-HTTLPR (Caspi et al., 2003; Kendler et al., 2005). The 5-HTTLPR is a polymorphic area in the promoter region of the serotonin transporter protein, SLC6A4. The serotonin transporter regulates the serotonin function in the brain, and thus, a polymorphism in this gene affects the rate of serotonin reuptake. The polymorphism on the 5-HTTLPR region has two common variations, either the short allele (s) or the long allele (l). The short allele results in reduced transcription for the serotonin transporter protein compared to the long allele. Individuals with two copies of the short allele have shown more depressive symptoms, diagnosable depression, suicidal tendencies, neuroticism, and amygdala reactivity to fearful stimuli than those who have one copy of the short allele or two copies of the long allele (Caspi et al., 2003; Kaufman et al., 2004; Lesch et al., 1996). However, the effect of more depressive symptoms is only present for those with a history of early adverse life experiences. Therefore, it is hypothesized that individuals with a short allele are characterized by the stable trait of neuroticism, but under conditions of early life stress, this neuroticism develops into psychopathology (Caspi et al., 2003). This evidence suggests a gene-environment interaction specifically for those with a history of early adverse life events. Although many researchers have confirmed the results of Caspi et al. (2003), other studies have observed this gene by environment interaction only for females (Barr et al., 2004). This suggests an interaction between the environment, gender, and genetics.

Gender

The role of gender in the development of psychopathology remains a major question for researchers. Researchers discovered that women are more likely to develop major depression after ELS. Thus, many researchers have questioned whether women experience more early life stressors or if there are neurobiological differences between the genders that contribute to a higher incidence of depression in women (Weiss et al., 1999). Researchers have indicated that the HPA axis in females is more sensitive than in males. For example, when under a psychosocial stress test, females demonstrate a greater magnitude and duration of activation in their HPA axis (Rhodes & Rubin., 1999). Sex steroids have also been targeted for their role in sensitizing females to stress and, as a result, becoming more vulnerable to depression. For instance, when men are treated with the female sex hormone, estradiol, they exhibit increased ACTH and cortisol responses to stress. Thus, females may have a sensitive reaction to stress due to estradiol and other sex hormones (Kirschbaum et al., 1996).

The impact of early life stress is mediated by the characteristics of ELS, and also by an

individual's genes and gender. By understanding the ways in which ELS can be moderated, researchers can understand how mental illnesses develop in those with a history of ELS and, as a result, devise strategies to prevent the development of MDD in those with a history of ELS. To make these interacting variables easier to analyze and interpret, researchers have developed a model to understand this phenomenon.

Working Model for the Effects of Various Factors on the Development of MDD

Due to the many factors contributing to the development of depression, Heim et al. (2004) adapted a working model for why some individuals develop depression in response to early life stress while others do not. Early life stress is associated with persistent sensitization of the stress response and alterations of the components in the HPA axis. However, these effects are moderated by environment and genetic factors, and thus, the working model that Heim et al. (2004) presents takes these factors into account. The early life stressors, (i.e. the frequency and timing of them) and the genome (i.e. the gender and genetic polymorphisms of an individual) contribute to the development of a vulnerable phenotype with alternations in the cortical-limbic-brainstem circuits. This phenotype will be more vulnerable based on certain characteristics of the ELS, genes, and gender. When trauma or stress occurs later in life, this vulnerable phenotype exhibits psychopathology including increased emotional, behavioral, and automatic responses. However, if treatment or social supports occur before the onset of psychopathology, reversing the HPA axis damages and maladaptive behavior may make an individual resilient to major depression and other mental illnesses. Many things can contribute to the development of psychopathology; it is therefore helpful to have a rough model that demonstrates how all of these factors interact to ultimately result in depression or not.

Treatments

Interventions in Childhood

By examining the working model by Heim et al. (2004), early treatments and interventions appear to be essential in preventing individuals with ELS from developing major depression later on in life. Both human and non-human studies have shown that environmental interventions have helped reverse the effects of early life stress. Maccari et al. (1996) demonstrated that early adoptions in rats, after having experienced prenatal stress, completely reversed the effects on the HPA axis. In collaboration with this research, Fisher et al. (2000) demonstrated that maltreated children who were placed in an early intervention foster care program showed significant improvement in behavioral adjustment and decreases in cortisol compared with children in normal foster care. The foster care program in this study promotes positive parenting strategies in which parents provide consistent, non-abusive discipline, high levels of positive reinforcement, and close monitoring and supervision of the child. Although the study is limited due to the small sample size, it still suggests that environmental interventions after the ELS are crucial for preventing the

long-term behavioral and neuroendocrine effects of ELS. This means reconstructing children's environment, so the caregivers are able to provide positive reinforcement, love, consistent discipline, and support. In cases of severe, ongoing abuse in early childhood, children should be placed in a foster home where more social support is provided. Treatments that are most effective are those that are put into effect early in the child's life; however since this is not always a possibility, there are other treatments that have been proven to be effective in treating MDD with a history of ELS.

Interventions in Adulthood

Early interventions should target the alternations in the HPA axis during its most plastic period – before ELS can produce more permanent changes. However, in many cases, early intervention is not possible, which leaves individuals vulnerable to develop major depression in adulthood. Although treatments for major depression have been used in the past to treat those with a history of ELS, recent research has suggested treatment specific options for those with a history of ELS and current MDD (Kehne et al., 2008; Nemeroff et al., 2003). Researchers compared the effects of Nefazodone, psychotherapy, or the combination of both (Nemeroff et al. 2003). Treatment response varied according to ELS status. Patients with current major depression but without ELS responded to combination treatment the best. However, those with current MDD and ELS were two times more likely to achieve remission when treated with psychotherapy alone than Nefazodone alone. Unlike those with MDD but without ELS, those with current MDD with ELS did not have any increase in treatment response to combination treatment (Nemeroff et al., 2003). This evidence presents psychotherapy as being crucial in treating those with a history of ELS. CRH 1 receptor antagonists are another treatment specific option for those with ELS because they are particularly suitable for hyperactive CRH 1 pathways. These drugs block the receptor sites for CRH and, as a result, block the secretion of ACTH and cortisol. Therefore, the drugs could be useful for reducing the consequences of sustained cortisol levels on hippocampal organization and volume and increasing treatment response by lessening the deleterious effects of chronic stressors (Kehne et al., 2008).

Further research is needed in this area in order to support the differentiation of treatments for those with MDD alone and those with MDD with a history of ELS. Previous research failed to look at this phenomenon from a developmental perspective, and this component of the research is critical in order to apply empirical, treatment specific options for those with MDD and ELS. Cross-sectional or longitudinal research looking at how the HPA axis functions in childhood, in adolescence, and in adulthood would help to support the idea that having a history of ELS damages the HPA axis and results in differing brain chemistry from that seen in individuals who have MDD without a history of ELS. It would also help to examine how the HPA axis, in those with ELS, is functioning at each developmental period. These results would show the changes in the effects of ELS throughout the lifespan.

Conclusion

Although those with a history of ELS begin to exhibit neurobiological effects that closely resemble those with MDD, there are distinct differences due to the early life stress occurring at such a vulnerable period in their lives. For instance, the chronic elevation of cortisol during

childhood results in the neurogenesis of many important organs, including the hippocampus. Other evidence includes increased CRH 1 receptors and decreased oxytocin concentrations in the cerebral spinal fluid of those with ELS. These all provide support for neurobiological effects specific to ELS. If research addresses the gaps identified in treatment research and produces the anticipated results, treatments may need to be altered in order to respond to the effects of ELS throughout developmental periods. However, in order for this to happen, more research is needed to provide more conclusive evidence. Therefore, longitudinal studies should be considered to discover the effects of abuse during different developmental periods. Also, new studies should divide groups based on the types of abuse to discover how these can have differential effects. However, it may be difficult because as studies have shown, abuse rarely occurs in pure forms. Lastly, studies investigating the effects of MDD should account for individuals with a history of ELS. Some of the studies examining the effects of MDD in the past could have been confounded because they did not take into consideration the number of individuals with ELS. It would be useful if these studies could be reviewed or even replicated to separate the effects of MDD and the effects of ELS. This area of research needs a significant amount of work, and it will be a long time before major improvements can be made. However, by separating the effects of ELS and MDD, clinicians may be able to treat these groups based on their specific behavioral and neurobiological needs.

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