



Review Article

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Lifestyle Factors Contributing to HPA-Axis Activation and Chronic Illness in Americans

Dawn Elise Snipes*

PhD, LPC-MHSP, LMHC Executive Director, AllCEUs.com, USA

*Corresponding author: Dawn-Elise Snipes, PhD, LPC-MHSP, LMHC Executive Director, AllCEUs.com, USA.

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Introduction

More than 50% of Americans suffer from one or more chronic conditions with an estimated cost of \$3.3 trillion annually including major depressive disorder (20%), generalized anxiety disorder (18.1%), low testosterone (25%) estrogen imbalances, diabetes (9.2%), hypertension, autoimmune disorders (23%), chronic pain, metabolic syndrome (30%), cardiovascular disease (44%) and hypothyroid (4.6%), all of which are associated with disturbances of the hypothalamic-pituitary-adrenal (HPA)-Axis. (National Center for Chronic Disease Prevention and Health Promotion 2019 [1-6].

The HPA-Axis

The hypothalamic-pituitary-adrenal (HPA)-axis is a key system involved in physiological homeostasis. [7]. It modulates and is modulated by a variety of inhibitory and excitatory systems. Some level of activation of the HPA-Axis is necessary for motivation and energy. When the HPA axis is activated in response to stress it impacts the balance of the neurotransmitters dopamine, serotonin, norepinephrine, GABA, and glutamate; modulates the release of inflammatory cytokines, estrogen and testosterone; and impacts insulin sensitivity and the balance of T3:T4 thyroid hormones. Sustained activation of this bidirectional system results in brain changes which alter hormones and monoamines (neurotransmitters) leading to further HPA-Axis activation and dysregulation. [8].

When exposed to a physical, environmental or social stressor, the HPA-Axis is activated and prompts the “fight or flight” reaction [6]. Neurons in the paraventricular nucleus (PVN) of the hypothalamus release corticotropin releasing factor (CRF) and arginine vasopressin (AVP) to stimulate the anterior pituitary gland to produce and secrete adrenocorticotrophic hormone (ACTH). ACTH causes glucocorticoid (cortisol) synthesis and release from

the adrenal glands as well as the release of activation of pro-inflammatory cytokines (IL-1, IL-4, IL-6, IL-18, and TNF- α) [9].

Cortisol's primary function is to increase blood glucose and modify fat and protein metabolism to fuel the fight or flight reaction and modulate immune and brain function to help the person effectively manage stressors [8]. It initially impacts the immune system and causes a potent anti-inflammatory response which allows the organism to react to the stressor without being hampered by the pain or fatigue. As cues of the threat wane, the body increases inflammation by releasing proinflammatory cytokines interleukin-1B IL-1, interleukin-6 (IL-6), and TNF- α , to accelerate wound healing caused by possible injury [6,10].

When compared to positive events, negative events, or “stress” causes greater awareness and recall of event details which leads to stronger encoding of negative or stressful events than pleasant events. According to the NEVER (Negative Emotional Valence Enhances Recapitulation) model of emotional valence, the greater the number of stimuli related to the unpleasant event that are remembered, the greater the likelihood that the person will encounter reminders of the event leading to increased recapitulation. This serves a survival function since there are more significant consequences to responding inappropriately or not protecting oneself from negative event. According to Dr. Aaron Ben-Zeev, people tend to perseverate on negative information and events five times more than positive ones [11,12]. Recapitulation initially leads to repeated HPA-Axis activation, but over time the continued stress prolongs the inflammatory response via continued activation of the HPA-Axis leading to glucocorticoid resistance causing cells to become less sensitive to cortisol to protect them from the persistent secretion. This is referred to as hypocortisolism.

Hypocortisolism allows for elevations in systemic inflammation to occur together with increases in cortisol. This prolonged

inflammation is associated with chronic conditions including arthritis, diabetes, obesity, heart disease, certain cancers, and Alzheimer's disease [6]. Other physiological changes that occur as a result of glucocorticoid resistance or hypocortisolism include...

- Disinhibition of corticotropin releasing hormone (CRH) and norepinephrine which lead to an exaggerated response to acute stressors and corresponding increase in cortisol [13].
- Exaggerated elevation of cortisol during exposure to acute stressors increases the sensitivity of NMDA receptors, which makes the brain generally more vulnerable to excitotoxic effects of stress [14].
- GABA (inhibitory) activity is decreased, and glutamate (excitatory) activity is increased [14].
- Thyroid hormones become imbalanced leading to abnormal T3:T4 ratio and increases in anxiety [14].
- Increased dopamine and norepinephrine levels increase arousal, startle response, fear memory encoding and increased HPA-Axis activation in response to recapitulation [14].
- The volume of the hippocampus which controls not only the HPA-Axis and stress responses, but also declarative memory is reduced due to the excitotoxic environment [14].
- Sustained HPA-Axis activation causes persistently high levels of CRH which eventually causes a blunting of the ACTH response to CRH stimulation [14].
- Serotonin levels are simultaneously decreased in parts of the brain disrupting communication between the amygdala and the hippocampus which leads to increased vigilance, startle, impulsivity, and memory intrusions, hostility, aggression, depression, and suicidally [14].
- Amygdala activity increases and promotes hypervigilance and impairs threat discrimination [14].
- Reduced prefrontal cortex volume impairs executive functioning and impulse control [14].
- Reduced anterior cingulate volume impairs the extinction of fear responses [14].
- Changes to the ratios of estrogen, testosterone and progesterone occur which impact the body's ability to modulate cortisol levels [15]. For example, studies have shown that ovariectomies reduce and estrogen replacements increase the reactivity of the HPA axis. The hypothalamic-pituitary-gonadal (HPG) and HPA axes work together to maintain species survival and minimize allostatic load [16]. Other studies have shown that prolonged psychological stress suppresses estrogen causing amenorrhea which has profound effects on cardiac, skeletal, psychological and reproductive systems [17].

In addition to the physiological changes that occur in response to glucocorticoid resistance, people in a state of hypocortisolism at the time of exposure to additional stressors develop stronger

trauma-related symptoms in part due to the exaggerated HPA-Axis response causing the stressor to have a stronger negative emotional valence [14]. People become stuck in this loop in which their basal cortisol and energy levels are low most of the time, yet when there is a stressor, the body's response is highly exaggerated which taxes the system and cause the body to stay in a state of hypocortisolism. Due to the heightened emotional valence of negative experiences and information and encoding of these memories, even exposure to positive experiences at a 1:1 ratio to negative ones does not "balance" the stress response.

Lifestyle Factors

It isn't just traumatic stress that activates the HPA-Axis though. When the body perceives a physiological, social, environmental threat including lack of quality sleep, excessive noise, poor nutrition, exposure to stimulants like caffeine, social stress, and hormone and neurohormone imbalances which can cause or result from chronic activation of the HPA-Axis, it triggers the HPA-Axis and the corresponding cascade of physiological changes [15]. Identification and modification of these so-called lifestyle factors can reduce chronic HPA-Axis activation and help prevent a myriad of chronic conditions. Some of the most pervasive stressors include the media, social media, sleep deprivation, sedentariness, obesity and poor nutrition. Since many mental illnesses have their onset in adolescence and early adulthood, possibly triggered by stress exposure in a vulnerable, developing brain, prevention is of the utmost importance [18].

Media

According to the social signal transduction theory of depression, perception of social threat by exposure social, symbolic, or imagined threats and adversity up-regulate the HPA-Axis. Modern media recasts social, cultural and political events and highlights our current vulnerabilities to terrorism and dystopia 24 hours a day [19]. The persistence of these messages within this climate of heightened awareness and vigilance about domestic and international terrorism, causes chronic HPA-Axis activation which leads to the release of proinflammatory cytokines that can trigger depressed mood, anhedonia, fatigue, psychomotor retardation, and behavioral withdrawal [6].

These messages are of increased concern regarding youth who, depending on their developmental level, may not be able to discern something that is being recast from something that is still occurring, setting the stage for generalized anxiety to develop [19]. The excitotoxic effects from frequent or persistent activation of the HPA-Axis in children is also of great concern, because, youth and adolescence is a time of rapid brain development making the brain more susceptible to injury. It is important to note that all people, not just adolescents, have a tendency to pay greater attention to and engage in more detailed cognitive processing of negative than positive information [20]. Therefore, exposure to the predominantly negative stories in the news results in increased negative emotional responses increasing HPA-Axis activation and anxiety-related behaviors [21].

Social Media

Social media is another example of a modern lifestyle factor that exposes people to social and symbolic threats and adversity. Social media has been defined as computer-mediated technology that allows one to create and share information and other forms of expression through virtual communities. In 2016, 98% of young adults used approximately 7.6 different social media regularly [22]. Individuals who spent more than 120 minutes on social media per day or who visited social media sites more than 9 times per day had significantly increased odds of depression [23,24]. Increased time online is associated with decline in communication with family members, a reduction of the internet user's social circle, a reduction in sleep and increased feelings of depression and loneliness [25]. All of these behaviors and symptoms are triggers for and can be symptoms of HPA-Axis dysregulation [26].

Another social stressor that is all too prevalent on social media is people who need to experience approval and reassurance through their social media connections "liking" their posts. When this does not happen, people who are more invested in social media often experience HPA-Axis activation as evidenced by poorer sleep quality, lower self-esteem and increased anxiety and depression. Stronger associations between technology-based SCFS and depressive symptoms for unpopular individuals [27,28].

Even people who are not seeking approval and validation can experience negative effects of social media. It is estimated that more than 50% of people have witnessed online hate in their "feeds" or in comments left on their posts. Approximately 10% have perpetrated online hate and 23% of people have been victimized by online hate [29].

Another way social media increases stress among young adults and adolescents is Fear Of Missing Out (FOMO). FOMO drives people to regularly check their social media feed to ensure they are not missing anything. This constant preoccupation with checking social media is associated with reduced work productivity, reduced involvement in real-life activities and relationships and higher anxiety when not online [30].

Even though social relationships are one of the greatest buffers against stress, social media relationships often do not provide the same benefits as real-life relationships [31]. Instead of enhancing social relationships, social media communication may lead to the mistaken impressions about physical appearance, success and happiness of other people, thus increasing feelings of jealousy (social threat) and depression [30,32,24]. Additionally, there is a strong positive correlation between amount of social media usage and perceptions of isolation [33]. Without a feeling of belonging from social relationships to help buffer against stress, people experience more distress and resultant HPA-Axis activation [34,35].

Sleep

Sleep, in particular lack of quality sleep, is another aspect of modern lifestyles which contributes to HPA-Axis activation and development of chronic illnesses. Deep sleep has an inhibiting

influence on the HPA axis, and activation of the HPA axis can lead to insomnia and 24 hour increases of ACTH and cortisol secretion [36]. Likewise, sleep disruption or deprivation can lead to significant increases of plasma cortisol levels, reduction in serotonin and melatonin and increases in norepinephrine which further impair the quality of sleep and lead to hyperactivation of the HPA-Axis [36-38].

According to the CDC, 1 in 3 adults does not get enough sleep [39]. There are many causes of sleep deprivation in American culture. Poor sleep hygiene including noisy sleep environments and blue light exposure; use of nicotine, alcohol or caffeine too close to bedtime and dependence upon sleep aids are among the most common.

Noise Related Sleep Disturbances

More than daytime noise, nighttime noise exposure causes more frequent awakening, less deep sleep and increased subjective disturbance and is correlated with an increased risk of HPA-Axis activation, cardiovascular disease, depression, anxiety. In fact, long-term nocturnal noise exposure >42decibels is associated with a 14% increase in prescriptions for sleep medication and a 17% increase in risk for being on antidepressant or anti-anxiety medications [40,41].

Nutrition Related Sleep Disturbances

A recent study of the 2007-2008 National Health and Nutrition Examination Survey (NHANES) found inadequate intake of vitamin A, calcium, selenium, carbohydrates, vitamin D, and lycopene to be associated with "poor sleep" and low levels of zinc and magnesium are implicated in the development of depression through overactivity of the HPA-Axis [42,43]. A significant negative correlation was found between sleep quality and low quality carbohydrate intake from processed foods [44].

Additionally, skipping breakfast and eating irregularly were strongly associated with hypoglycemia which can cause chronic HPA-Axis activation and poor sleep quality [44,45].

Environmentally Related Sleep Disturbances

Another factor impacting sleep is working in buildings with lack of access to natural light, shift work and overnight work which prohibits the body from receiving cues from the environment which would regulate a 24-hour circadian rhythm. Nearly 20% of Americans are at risk for "graveyard shift work disorder" which is characterized by insomnia and daytime drowsiness. Insomnia at night causes people to experience frustration and increases stress because the person was drowsy all day and desperately wants to sleep but cannot. Daytime drowsiness also causes people to use stimulants to wake up or get energy throughout the day contributing to even more HPA-Axis activation [46].

The ubiquitous presence of blue light from digital devices and televisions is yet another modifiable lifestyle factor. Blue light disrupts the signals to the brain that trigger the production of melatonin. While this may not lead to as much frustration as

insomnia, the reduction in duration of quality sleep will also trigger the stress response [36].

Snoring and Apnea Related Sleep Disturbances

According to the American Academy of sleep medicine, 26% of adults have sleep apnea which is associated with HPA axis activation [47]. While there are not a lot of ways to prevent sleep apnea, use of a CPAP device has been shown to reduce HPA-Axis activation via reduced cortisol levels [48].

Alcohol Related Sleep Disturbances

According to the Centers for Disease Control (CDC), heavy drinking is defined as drinking more than 15 drinks per week for men and more than 8 drinks a week for women (CDC, 2018). Twenty percent (20%) of Americans are heavy drinkers and 50% of heavy drinkers drink more than 10 alcoholic beverages each day [49]. Alcohol stimulates the hypothalamic-pituitary-adrenal (HPA) axis, via the hypothalamus, and repeated alcohol exposure leads to a blunted HPA-Axis response which is associated with depressive symptoms such as anhedonia, fatigue and behavioral withdrawal as well as widespread inflammation and increases the risk for development of other chronic health problems [50].

Many people use alcohol specifically to help them “wind down” so they can get to sleep. While it is true that alcohol decreases the time it takes for people to fall asleep (sleep latency), and increases the quality and quantity of NREM sleep during the first half of the night, during the second half of the night sleep, as the depressant effects of the alcohol wears off, sleep becomes disrupted [51]. Within the USA, it is estimated that societal costs of alcohol-related sleep disorders exceeds \$18 billion [51,52].

Nicotine Related Sleep Disturbances

Nicotine use is pervasive in the United States. Recently with the introduction of e-cigarettes, more and younger people have begun using nicotine products [53]. The blunting of the HPA-Axis response in the face of persistent exposure to a stimulant (nicotine) is evident in the findings that recent nicotine use and lower dependence is associated with increased activation of the HPA-Axis, but as dependence goes up, response of the HPA-Axis decreases [54]. Research has also found a significant reciprocal, relationships between smoking and sleep disturbances. The stimulant effects of nicotine may intensify sleep problems and be used during waking hours to counteract the effects of sleep problems on cognitive function [55,56].

Caffeine Related Sleep Disturbances

Caffeine is found not only in coffee, but also soda, chocolate, over the counter migraine medications, decongestants and some diet and workout supplements. Like other stimulants, caffeine has been found to cause a significant increase in cortisol levels. Interestingly, when caffeine was paired with a mental or physical stressor, cortisol and adrenaline levels exceeded levels seen when caffeine or stressors were encountered independently [57,58].

Malnutrition

We already discussed the impact of nutritional deficiencies, eating low quality carbohydrates, skipping breakfast and erratic eating patterns on sleep quality and resultant HPA-Axis activation. However, nutritional deficits are implicated in a host of other problems that can dysregulate the HPA-Axis. Up to 95% of some neurotransmitters are made in the gut [59]. Recently scientists have discovered the gut-brain axis which is a bi-directional system between the brain and gastrointestinal tract, that links emotional and cognitive centers of the brain with the digestive tract via the vagus nerve [60]. The influence of gut bacteria on behavior is becoming increasingly understood, introducing the possibility that alterations in gut bacteria may be important in the development of disorders of the nervous system including HPA-Axis dysregulation. A healthy gut microbiome has over 1000 species of bacteria and can decrease depression and anxiety, regulate sleep, appetite and improve cognition [61]. An unhealthy gut microbiome contributes to an exaggerated HPA-Axis response [61,62]. Additionally, a healthy diet that supports the creation of hormones and neurotransmitters will help the body regulate the balance between excitatory (e.g., norepinephrine, dopamine, and glutamate) and inhibitory (e.g., serotonin and GABA) neurotransmitters and positively affect neurological, emotional and behavioral responses [63]. Many of the hormones and neurotransmitters in the body are constructed from proteins (amino acids) with the help of carbohydrates, vitamins and minerals. Without adequate intake of these nutrients, the body cannot create norepinephrine, corticotropin releasing factor (CRH), serotonin, glutamate, dopamine and many more.

Serotonin is an inhibitory neurotransmitter which helps stabilize mood, downregulate the HPA-Axis and is broken down to create melatonin to promote sleep. It is constructed from the amino acid tryptophan with the help of iron, magnesium, vitamin B6, folic acid, vitamin C and zinc. Insufficient levels of any of these nutrients can lead to serotonin depletion and hamper the body's ability to down-regulate the HPA-Axis. Additionally, frequent intake of caffeine or other stimulants can cause serotonin levels to become depleted [64]. Another neurochemical, GABA is also an inhibitory neurotransmitter which is constructed from the amino acid glutamine with the help of vitamin B6. When either of these two nutrients is insufficient, the HPA-Axis will stay activated until sustained activation triggers the conservation response of hypocortisolism.

Sedentariness

Americans are becoming increasingly sedentary [65]. As stress levels increase, it is important to find ways to reduce related inflammation and oxidative stress from HPA-Axis activation to prevent chronic conditions. Exercise has been shown to moderate both inflammatory cytokines and oxidative stress [66]. Low intensity exercise (at 40% VO2max) has even been shown to reduce cortisol levels and increase serotonin contributing to the relaxation response [67,68].

Additionally, research has demonstrated that unfit individuals have increased HPA, inflammatory, and cardiovascular reactivity indicating that individuals who maintain sedentary lifestyle may have slower recovery from acute stress [69-72]. These studies support the idea that exercise can reduce the consequences of HPA Axis activation [73-75].

Summary

While some stress is necessary for energy and motivation, and some stress in life is inevitable, frequent or persistent stress is toxic to our bodies producing a host of physiological changes that can cause chronic health problems including mood disorders, metabolic syndrome, diabetes, chronic pain, auto-immune disorders and hypothyroidism. These changes have a bidirectional influence on the HPA-Axis. Under conditions of stress, pain or inflammation, the HPA-Axis is activated. When the HPA-Axis is activated too much, it can produce inflammation, anxiety and depressive symptoms. Several factors that are common to the American lifestyle including being inundated with information about threats to our social welfare from the news media, excessive engagement with and exposure to disinhibition on social media, insufficient quality sleep, poor nutrition, use of alcohol, nicotine and caffeine and sedentariness significantly contribute to the persistent activation of the HPA-Axis. Each of these factors is completely modifiable and can reduce the demands on the HPA-Axis as well as ensure it has all of the building blocks it needs to function effectively.

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Conflict of Interest

No conflict of interest.

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