THE GOOD, THE BAD, AND THE CORTISOL

By **Christina Ennis**

Think about the last time you felt stressed. Did your heart beat faster? Did your stomach tie into knots? Maybe your hands went cold, or possibly started shaking? The brain is in control of all of these physiological changes, and is actually trying to help you survive what it interprets as a potentially life-threatening situation. It's commonly thought of as the fight-or-flight response; either your body prepares to run away from the problem or readies itself to stay and tackle the threat.

The pathway in charge of this response is known as the hypothalamic-pituitary-adrenal axis, or the HPA axis for short (see Figure 1). It is so important for survival that it has been conserved by evolution, appearing in some form in even the earliest of vertebrate species (Denver, 2009). The HPA axis consists of a complicated series of steps that begin in the hypothalamus, where a specific group of cells secrete corticotropin-releasing hormone. This hormone is then able to travel through the brain to reach the pituitary, which is the pea-sized gland sitting just behind the bridge of the nose. Once the corticotropin-releasing hormone interacts with this gland, it stimulates the release of adrenocorticotropic hormone. Because of the location of the pituitary, adrenocorticotropic hormone is able to be transported throughout the body until it eventually finds cells on the adrenal cortex with which it can interact. This hormone works to stimulate the production of the steroid hormone cortisol. Once cortisol enters the bloodstream, it has significant effects all over the body.

The Many Roles of Cortisol

Cortisol greatly impacts both metabolism and digestion. Specifically, it is associated with glucose, the sugar that converts into every cell's energy supply known as adenosine triphosphate. Cortisol, by influencing gene transcription, stimulates gluconeogenesis, which is the process of forming glucose from precursors other than carbohydrates, during periods of fasting (Khani & Tayek, 2001). This response allows the liver to use glucose that the peripheral tissue does not need and converts it into liver glycogen, thus preparing the body should it encounter a food shortage and starvation (Barcellos et al., 2010). In addition, cortisol plays an important, though indirect, role in both liver and muscle glycogenolysis, which is the breakdown of glycogen once the body needs to use its stored glucose (Barcellos et al., 2010; Coderre et al., 1991). Cortisol is able to do this by influencing and interacting with glucagon, the hormone that regulates the usage of glucose (Lecavalier et al., 1990). Because of the many interactions between cortisol and glucose, researchers believed and have, ultimately, demonstrated that HPA axis activity is enhanced in many patients with diabetes (Chiodini et al., 2015).

Besides affecting glucose processes, cortisol influences electrolyte balance. Cortisol is a diuretic, preventing cells from losing

Did You Know?

Some scientists believe that cortisol's original purpose may have been sodium transport. They have found that freshwater fish use a cortisol-based system to bring sodium in, whereas saltwater fish use it to expel extra salt (Laurent & Perry, 1990; Maetz et al., 1967).

sodium as well as promotes potassium excretion, thus helping to regulate bodily pH (Knight et al., 1955). Maintaining a pH between 6.0 and 7.5 is important because of the negative consequences of having too much acid, known as metabolic acidosis, or bicarbonate, known as alkalosis, in the blood, which range from muscle twitches to lung collapse (Arruda & Kurtzman, 1977).

Cortisol also affects the immune system. It prevents the release of substances that cause inflammation, such as IL-12, interferon, IFN-gamma, and TNF-alpha, by antigen-presenting cells and Th1 cells, while also upregulating anti-inflammatory substances, such as IL-4, IL-10, and IL-13, by Th2 cells (Elenkov, 2004; Franchimont, 2004). Because of these effects, cortisol is often used to treat conditions such as rheumatoid arthritis, vasculitis, lupus, and allergies, as well as skin problems like rashes and eczema (Vane & Botting, 1987).

Circadian rhythm is also greatly impacted by cortisol. Normal cortisol secretion, meaning when it is not induced by the activation of the HPA axis, undergoes diurnal variation: the levels peak around 8:00am and bottom out around midnight (Chung et al., 2011). This pattern contrasts that of melatonin secretion, with melatonin being the hormone responsible for regulating sleepiness and wakefulness. In the morning, melatonin levels are low, and eventually rise at night once the brain's pineal gland is activated by the hypothalamus (Monteleone et al., 1992). Researchers have found that cortisol and melatonin actually work to counteract each other, with a high concentration of one inhibiting the activity of the other (Monteleone et al., 1992; Zisapel et al., 2005).

Finally, cortisol works to inhibit the further production of itself in a negative feedback loop (see Figure 2). The presence of high concentrations of the hormone within the bloodstream inhibit the release of both more corticotropin-releasing hormone and more adrenocorticotropic hormone (Gold et al., 2002; Wood & Rudolph, 1983). There are similar points of negative feedback along the HPA axis, namely how high concentrations of adrenocorticotropic hormone prevents the secretion of additional corticotropin-releasing hormone (Abelson et al., 2007; Yehuda et al., 2006). These loops exist because of the dangers associated with high levels of cortisol, and actively work to ensure that these levels are not reached.

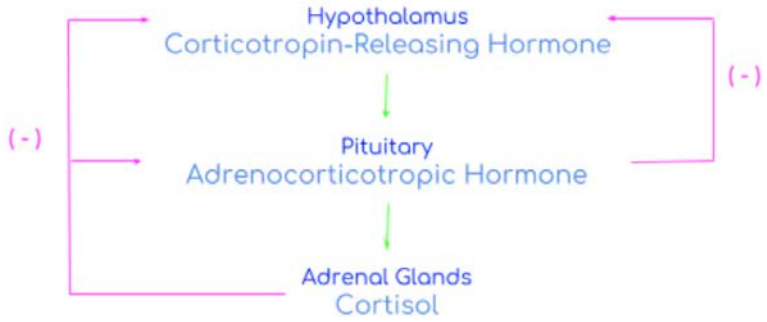

Figure 2 Here, you can see the many negative feedback loops (pictured in pink) involved in the HPA axis. Created by Christina Ennis.

Stress and Development

Researchers have found that prenatal stress can influence HPA axis regulation after birth and later in life. In animal experiments, exposure to prenatal stress causes a hyperreactivity of the HPA axis. Prenatally stressed rats, for example, have higher basal levels of corticosterone, their version of cortisol, as well as abnormal circadian rhythms (Koehl et al., 1999). They also require a longer period of time after the presence of a stressor for their hormone levels to return to their baseline. Other studies have demonstrated that prenatally stressed animals have high blood glucose levels, as well as have fewer glucocorticoid receptors in some areas of the brain (Weinstock et al., 1992). Switching over to human studies, there is growing evidence that prenatal stress impacts HPA axis regulation. Children that were stressed prenatally have been shown exhibit abnormal cortisol rhythms (Glover et al., 2010; Gutteling et al., 2005). Additionally, prolonged maternal stress is associated with mild impairments of intellectual activity and language development in their children, and is linked to disorders such as attention deficit hyperactivity disorder, schizophrenia, anxiety, and depression (Weinstock, 2008).

However, the effect of early

life stress on HPA axis functioning is less understood. Differing levels of stress seem to have opposing effects later in life: exposure to mild or moderate stressors early in life enhance HPA regulation whereas early-life exposure to extreme or prolonged stress can induce hyperreactivity of the HPA axis and thus contributes to a lifelong vulnerability to stress (Flinn et al., 2011; Liu et al., 1997). Several mechanisms have been proposed to explain these conflicting impacts of stress. Some believe that there is a critical period of development in which the levels of stress hormones within the bloodstream permanently calibrate the functioning of the HPA axis (Champagne et al., 2003; Macrì & Würbel, 2006). Others, however, hypothesize that such effects are mediated by maternal care, either through inducing epigenetic changes or promoting a sense of calmness in the offspring (Champagne et al., 2003; de Kloet et al., 2005; Schechter et al., 2015). Whatever the cause, prolonged early life stress is thought to sensitize the HPA axis, thus resulting in the hypersecretion of the various hormones involved in the pathway. This aspect of sensitization is supported by the findings that adulthood victims of childhood abuse have increased concentrations of adrenocorticotropic hormone and corticotropin-releasing hormone after exposure to a psychosocially stressful event (Heim et al., 2001).

Did You Know?

Yoga and meditation have proved to be effective techniques in reducing stress and regulating HPA axis stimulation. It also triggers alpha brain wave activity, which is thought to promote relaxation and creativity while minimizing depression (Kamei et al., 2000).

Hyperactivity of the HPA Axis

You may be wondering why non-life-threatening events, such as a meeting with a boss or a final exam, are able to trigger the activation of the HPA axis, and thus the production of cortisol, in some people. In the face of periods of severe stress during adulthood, such as those caused by negative work or family relationships or combat exposure for example, the dynamics of the HPA axis change (Stephens & Wand, 2012). Specifically, chronic stress triggers a shift in the normal diurnal release of cortisol as well as in the stress-induced levels of this hormone (Juster et al., 2011; McEwen, 2007; Stephens & Wand, 2012). In short, this means that chronic stress increases the baseline levels of cortisol in the body while also increasing the sensitivity of the HPA axis, resulting in its activation during times where typically it would and should not be. It is here, when the HPA axis is inappropriately or persistently activated, where problems start to arise.

Clearly, the hyperactivity of the HPA axis has a role in anxiety disorders. Anxiety disorders, including generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, and social phobias, are the most common psychiatric illnesses, affecting up to 33.7% of the population (Bandelow & Michaelis, 2015). Often, these maladies are treated with drugs such as selective serotonin-reuptake inhibitors and benzodiazepines, which work by altering the levels of neurotransmitters able to interact with brain cells. However, researchers have identified a secondary action of these drugs: they correct HPA axis hypersensitivity (Lenze et al., 2011; Lopez et al., 1990). These findings are significant because the process of directly assessing HPA axis functioning is difficult and complex. Since this pathway is activated during stress, measuring cortisol levels in the bloodstream after exposure to various triggers would be too specific to each individual since not everyone has the same reaction to the same stimuli, if not cruel to all of the participants of the study. Therefore, the ability to study HPA axis dysfunctioning in patients with anxiety disorders through their treatment plans is optimal.

In addition, the HPA axis has been shown to dysfunction during psychotic episodes. One model of psychosis posits that predisposing biological factors make some individuals more sensitive to stress, and thus more vulnerable to developing psychosis after stressful events (Mondelli et al.,

Did You Know?

Caffeine stimulates the release of cortisol. However, if you consume moderate levels of caffeine, meaning 300 mg, or three cups of brewed coffee, daily, then cortisol secretion is less than if you do not (Lovallo et al., 2008).

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2010). Following this assumption, first-episode psychosis patients display HPA axis hyperactivity and high basal levels of cortisol, acting as both a causal and exacerbating factor of their clinical symptoms as well as cognitive impairments (Gallagher et al., 2007; Herz et al., 1985; Lammers et al., 1995; Sachar et al., 1970; Tandon et al., 1991). However, some theorize that this hyperactivity contributes to the pathogenesis of psychotic disorders by increasing brain dopaminergic activity (Mondelli et al., 2010; Walker & Diforio, 1997). This idea is supported by the fact that antipsychotic drugs, in addition to regulating dopamine levels, have a secondary function of lowering HPA axis activity (Cohrs et al., 2006; Lammers et al., 1995; Mondelli et al., 2010).

HPA dysregulation has been identified in many other mental health disorders. In particular, depression has been extensively studied as cortisol has a multifaceted role in its symptomatology. In over half of the cases of major depression, the diurnal rhythms of this hormone is disturbed and the negative feedback loops that prevent its accumulation are nonfunctional (Burke et al., 2005; Herbert, 2012). Additionally, patients with major depression have been shown to have significantly higher levels of cortisol than in those with either panic disorder and schizophrenia (Yehuda et al., 1993). It is thought that cortisol contributes to major depression by altering the volume and metabolism of various brain regions, including the prefrontal cortex, the amygdala, and the hippocampus (Gold et al., 2002). Interestingly, cortisol has been shown to activate the genetic basis of major depression in the same way as environment events amplify the risk of this disorder, with its influence beginning prenatally but continuing into adulthood (Herbert, 2012).

However, there is a disease in which cortisol hypersecretion is present without a hypersensitivity of the HPA axis: Cushing's syndrome. This disease, though rare since it affects on average only one person per million per year, can have devastating effects on the health of those affected by it (Sharma et al., 2015). Cushing's syndrome is usually caused by a tumor somewhere along the HPA axis, such as on the pituitary or adrenal glands, or is induced by high levels of exogenous glucocorticoid exposure, as is the case in some patients with autoimmune disorders. The treatment options for this disease are limited, with surgeries resulting in complete remission in 60% of cases (Sharma et al., 2015).

Hypoactivity of the HPA Axis

At this point, you may be thinking that cortisol is a dangerous hormone, and that less of it would lead to a healthier and happier life. However, this is not always the case. There is a life-threatening disease, known as adrenal insufficiency or Addison's disease, in which the adrenal glands do not function properly, resulting in the body producing too little cortisol. Affecting only 100 people per million, it impairs quality of life by causing problems with circadian rhythm, weight loss, low blood pressure and sugar, as well as triggering stomach issues (Bensing et al., 2016).

Just as in hyperactivity, there are also disorders in which the HPA axis is abnormally inactive. Perhaps the most common of these is chronic fatigue syndrome, as it affects nearly 5% of the population (Johnston et al., 2013). Researchers have demonstrated that the HPA axis in patients with this disease have low basal evening levels of cortisol, yet high basal evening levels of adrenocorticotropic hormone, and even hypothesize that the disease is in fact caused by problems in this pathway (Demitrack et al., 1991).

The Bottom Line

Clearly, the HPA axis has a signif-

icant impact on multiple aspects of both physiological and mental health. Though cortisol gets a bad reputation, with multiple vitamin and drug companies claiming that it is at the root of any issue you may encounter, this is not true. It is only in the presence of chronically high or low levels of this stress hormone where such problems arise. However, that does not mean to say that stressful periods are in isolation healthy. While they are necessary for both motivation and even survival, times of stress can result in discomfort and ultimately lead to the development of various disorders, including anxiety and depression. So, the next time you notice that you're feeling stressed, take into account the processes going on within your body and the damage you may be causing if you let stressors affect you too much.

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