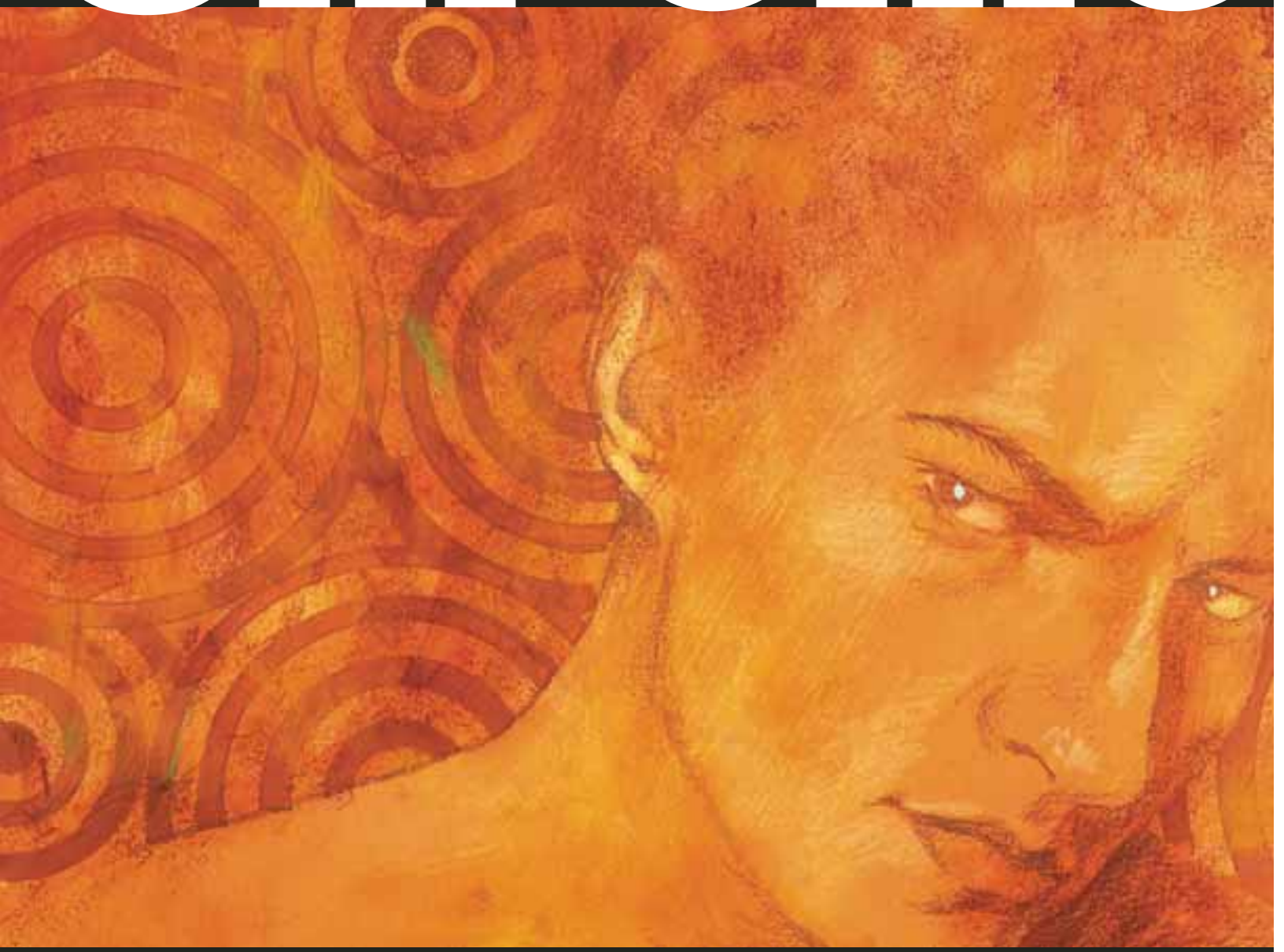
Chronic



MELISSA BRADDOCK AND ROBERT BOCK

Stress AND STRESS DISORDERS

THE EFFECTS OF STRESS SYSTEM MALFUNCTION

Whether from a charging lion, or a pending deadline, the body's response to stress can be both helpful and harmful. The stress response gives us the strength and speed to ward off or flee from an impending threat. But when it persists, stress can put us at risk for obesity, heart disease, cancer, and a variety of other illnesses.

Perhaps the greatest understanding of stress and its effects has resulted from a theory by George Chrousos, MD, Chief of the Pediatric and Reproductive Endocrinology Branch at the National Institute of Child Health and Human Development (NICHD), and Philip Gold, MD, of the Clinical Neuroendocrinology Branch at the National Institute of Mental Health (NIMH).

Introduction

A threat to your life or safety triggers a primal physical response from the body, leaving you breathless, heart pounding, and mind racing. From deep within your brain, a chemical signal speeds stress hormones through the bloodstream, priming your body to be alert and ready to escape danger. Concentration becomes more focused, reaction time faster, and strength and agility increase. When the stressful situation ends, hormonal signals switch off the stress response and the body returns to normal.

But in our modern society, stress doesn't always let up. Many of us now harbor anxiety and worry about daily events and relationships. Stress hormones continue to wash through the system in high levels, never leaving the blood and tissues. And so, the stress response that once gave ancient people the speed and endurance to escape life-threatening dangers runs constantly in many modern people and never shuts down.

Research now shows that such long-term activation of the stress system can have a hazardous, even lethal effect on the body, increasing risk of obesity, heart disease, depression, and a variety of other illnesses.

Much of the current understanding of stress and its effects has resulted from the theory by Chrousos and Gold. Their theory explains the complex interplay between the nervous system and stress hormones-the hormonal system known as the hypothalamic-pituitary-adrenal (HPA) axis. Over the past 20 years, Chrousos and his colleagues have employed the theory to understand a variety of stress-related conditions, including depression, Cushing's syndrome, anorexia nervosa, and chronic fatigue syndrome.

The stress circuit

The HPA axis is a feedback loop by which signals from the brain trigger the release of hormones needed to respond to stress. Because of its function, the HPA axis is also sometimes called the "stress circuit."

Briefly, in response to a stress, the brain region known as the hypothalamus releases corticotropin-releasing hormone (CRH). In turn, CRH acts on the pituitary gland, just beneath the brain, triggering the release of another hormone, adrenocorticotropin (ACTH) into the bloodstream. Next, ACTH signals the adrenal glands, which sit atop the kidneys, to release a number of hormonal compounds.

These compounds include epinephrine (formerly known as adrenaline), Norepinephrine (formerly known as noradrenaline) and cortisol. All three hormones enable the body to respond to a threat. Epinephrine increases blood pressure and heart rate, diverts blood to the muscles, and speeds reaction time. Cortisol, also known as glucocorticoid, releases sugar (in the form of glucose) from the body reserves so that this essential fuel can be used to power the muscles and the brain.

Normally, cortisol also exerts a feedback effect to shut down the stress response after the threat has passed, acting upon the hypothalamus and causing it to stop producing CRH.

This stress circuit affects systems throughout the body. The hormones of the HPA axis exert their effect on the autonomic nervous system, which controls such vital functions as heart rate, blood pressure, and digestion.

The HPA axis also communicates with several regions of the brain, including the limbic system, which controls motivation and mood, with the amygdala, which generates fear in response to danger, and with the hippocampus, which plays an important part in memory formation as well as in mood and motivation. In addition, the HPA axis is also connected with brain regions that control body temperature, suppress appetite, and control pain.

Similarly, the HPA axis also interacts with various other glandular systems, among them those producing reproductive hormones, growth hormones, and thyroid hormones. Once activated, the stress response switches off the hormonal systems regulating growth, reproduction, metabolism, and immunity. Short term, the response is helpful, allowing us to divert biochemical resources to deal with the threat.

Stress, heredity, and the environment

According to Chrousos, this stress response varies from person to person. Presumably, it is partially influenced by heredity. For example, in most people the HPA axis probably functions appropriately enough, allowing the body to respond to a threat, and switching off when the threat has passed. Due to differences in the genes that control the HPA axis, however, other people may fail to have a strong enough response to a threat, while still others may over respond to even minor threats.

Beyond biological differences, the HPA axis also can alter its functioning in response to environmental influences. The HPA axis may permanently be altered as a result of extreme stress at any time during the life cycle—during adulthood, adolescence, early childhood, or even in the womb.

If there are major stresses in early childhood, the HPA feedback loop becomes stronger and stronger with each new stressful experience. This results in an individual who, by adulthood, has an extremely sensitive stress circuit in place. In life threatening situations—such as life in an area torn by war—this exaggerated response would help an individual to survive. In contemporary society, however, it usually causes the individual to overreact hormonally to comparatively minor situations.

Effects on the body

The reproductive system

Stress suppresses the reproductive system at various levels, says Chrousos. First, CRH prevents the release of gonadotropin releasing hormone (GnRH), the "master" hormone that signals a cascade of hormones that direct reproduction and sexual behavior. Similarly, cortisol and related glucocorticoid hormones not only inhibit the release of GnRH, but also the release of luteinizing hormone, which prompts ovulation and sperm release. Glucocorticoids also inhibit the testes and ovaries directly, hindering production of the male and female sex hormones testosterone, estrogen, and progesterone.

The HPA overactivity that results from chronic stress has been shown to inhibit reproductive functioning in anorexia nervosa and in starvation, as well as in highly trained ballet dancers and runners. For example, in one study, Chrousos found that men who ran more than 45 miles per week produced high levels of ACTH and cortisol in response to the stress of extreme exercise. These male runners had low LH and testosterone levels. Other studies have shown that women undertaking extreme exercise regimens had ceased ovulating and menstruating.

However, the interaction between the HPA axis and the reproductive system is also a two way street. The female hormone estrogen exerts partial control of the gene that stimulates CRH production. This may explain, why, on average, women have slightly elevated cortisol levels. In turn, higher cortisol levels, in combination with other, as yet unknown, factors, may be the reason why women are more vulnerable than men to depression, anorexia nervosa, panic disorder, obsessive compulsive disorder, and autoimmune diseases like lupus and rheumatoid arthritis.

Growth

The hormones of the HPA axis also influence hormones needed for growth. Prolonged HPA activation will hinder the release of growth hormone and insulin-like growth factor 1 (IGF-1), both of which are essential for normal growth. Glucocorticoids released during prolonged stress also cause tissues to be less likely to respond to IGF-1. Children with Cushing's syndrome—which results in high glucocorticoid levels—lose about 7.5 to 8.0 centimeters from their adult height.

Similarly, premature infants are at an increased risk for growth retardation. The stress of surviving in an environment for which they are not yet suited, combined with the prolonged stress of hospitalization in the intensive care unit, presumably activates the HPA axis. Growth retarded fetuses also have higher levels of CRH, ACTH, and cortisol, probably resulting from stress in the womb or exposure to maternal stress hormones.

Old research has also shown that the stress from emotional deprivation or psychological harassment may result in the short stature and delayed physical maturity of the condition known as psychosocial short stature (PSS).

PSS was first discovered in orphanages, in infants who failed to thrive and grow. When these children were placed in caring environments in which they received sufficient attention, their growth resumed. The children's cortisol levels were abnormally low, a seeming contradiction, which Chrousos investigated by studying a small, non-human primate, the common marmoset. These monkeys live in small family groups in which infants are cared for by both parents. As in human society, the infants are sometimes well cared for, but sometimes abused. Like humans, the abused monkeys showed evidence of PSS.

The researchers determined that the stressed and abused monkeys appeared to respond normally to stress, but seemed unable to "switch off" the stress response by secreting appropriate cortisol levels, thereby remaining in a state of prolonged stress arousal as compared to their peers.

The gastrointestinal tract

As many of us know, stress can also result in digestive problems. The stress circuit influences the stomach and intestines in several ways. First, CRH directly hinders the release of stomach acid and emptying of the stomach. Moreover, CRH also directly stimulates the colon, speeding up the emptying of its contents. In addition to the effects of CRH alone on the stomach, the entire HPA axis, through the autonomic nervous system, also hinders stomach acid secretion and emptying, as well as increasing the movement of the colon.

Also, continual, high levels of cortisol—as occur in some forms of depression, or during chronic psychological stress—can increase appetite and lead to weight gain. Rats given high doses of cortisol for long periods had increased appetites and had larger stores of abdominal fat. The rats also ate heavily when they would normally have been inactive. Overeating at night is also common among people who are under stress.

The immune system

The HPA axis also interacts with the immune system, making you more vulnerable to colds and flu, fatigue and infections.

In response to an infection, or an inflammatory disorder like rheumatoid arthritis, cells of the immune system produce three substances that cause inflammation: interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor (TNF). These substances, working either singly or in combination with each other, cause the release of CRH. IL-6 also promotes the release of ACTH and cortisol. Cortisol and other compounds then suppress the release of IL-1, IL-6, and TNF, in the process switching off the inflammatory response.

Ideally, stress hormones damp down an immune response that has run its course. When the HPA axis is continually running at a high level, however, that damping down can have a down side, leading to decreased ability to release the interleukins and fight infection.

In addition, the high cortisol levels resulting from prolonged stress could serve to make the body more susceptible to disease, by switching off disease-fighting white blood cells. Although the necessary studies have not yet been conducted, Chrousos considers it possible that this same deactivation of white blood cells might also increase the risk for certain types of cancer.

Conversely, there is evidence that a depressed HPA axis, resulting in too little corticosteroid, can lead to a hyperactive immune system and increased risk of developing autoimmune diseases—diseases in which the immune system attacks the body's own cells. Overactivation of the antibody-producing B cells may aggravate conditions like lupus, which result from an antibody attack on the body's own tissues.

Stress-related disorders

One of the major disorders characteristic of an overactive HPA axis is melancholic depression. Chrousos' research has shown that people with depression have a blunted ability to "counterregulate," or adapt to the negative feedback of increases in cortisol. The body turns on the "fight or

flight" response, but is prevented from turning it off again. This produces constant anxiety and overreaction to stimulation, followed by the paradoxical response called "learned helplessness," in which victims apparently lose all motivation.

Hallmarks of this form of depression are anxiety, loss of appetite, loss of sex drive, rapid heart beat, high blood pressure, and high cholesterol and triglyceride levels. People with this condition tend to produce higher-than-normal levels of CRH. The high levels of CRH are probably due to a combination of environmental and hereditary causes, depending on the person affected.

However, rather than producing higher amounts of ACTH in response to CRH, depressed people produce smaller amounts of this substance, presumably because their hippocampuses have become less sensitive to the higher amounts of CRH. In an apparent attempt to switch off excess CRH production, the systems of people with melancholic depression also produce high levels of cortisol. However, by-products of cortisol, produced in response to high levels of the substance, also depress brain cell activity. These by-products serve as sedatives, and perhaps contribute to the overall feeling of depression.

Other conditions are also associated with high levels of CRH and cortisol. These include anorexia nervosa, malnutrition, obsessive-compulsive disorder, anxiety disorder, alcoholism, alcohol and narcotic withdrawal, poorly controlled diabetes, childhood sexual abuse, and hyperthyroidism.

The excessive amount of the stress hormone cortisol produced in patients with any of these conditions is responsible for many of the observed symptoms. Most of these patients share psychological symptoms including sleep disturbances, loss of libido, and loss of appetite as well as physical problems such as an increased risk for accumulating abdominal fat and hardening of the arteries and other forms of cardiovascular disease. These patients may also experience suppression of thyroid hormones, and of the immune system. Because they are at higher risk for these health problems, such patients are likely to have their life spans shortened by 15 to 20 years if they remain untreated.

Although many disorders result from an overactive stress system, some result from an under active stress system. For example, in the case of Addison's disease, lack of cortisol causes an increase of pigment in the skin, making the patient appear to have a tan. Other symptoms include fatigue, loss of appetite, weight loss, weakness, loss of body hair, nausea, vomiting, and an intense craving for salt. Lack of the hormone CRH also results in the feelings of extreme tiredness common to people suffering from chronic fatigue syndrome. Lack of CRH is also central to seasonal affective disorder (SAD), the feelings of fatigue and depression that plague some patients during winter months.

The body's response to stress can be both helpful and harmful.

Chrousos and his team, showed that sudden cessation of CRH production may also result in the depressive symptoms of postpartum depression. In response to CRH produced by the placenta, the mother's system stops manufacturing its own CRH. When the baby is born, the sudden loss of CRH may result in feelings of sadness or even severe depression for some women.

Recently, Chrousos and his coworkers uncovered evidence that frequent insomnia is more than just having difficulty falling asleep. The researchers found that, when compared to a group of people who did not have difficulty

falling asleep, the insomniacs had higher ACTH and cortisol levels, both in the evening and in the first half of the night. Moreover, the insomniacs with the highest cortisol levels tended to have the greatest difficulty falling asleep.

The researchers theorized that, in many cases, persistent insomnia may be a disorder of the stress system. From their ACTH and cortisol levels, it appears that the insomniacs have nervous systems that are on overdrive, alert and ready to deal with a threat, when they should otherwise be quieting down. Rather than prescribing drugs known as hypnotics to regulate the sleep system, the researchers suggested that physicians might have more success prescribing antidepressants, to help calm an overactive stress system. Behavior therapy, to help insomniacs relax in the evening, might also be useful.

After conducting many years of research into the functioning of the HPA axis, Chrousos concluded that chronic stress should not be taken lightly or accepted as a fact of life.

"Persistent, unremitting stress leads to a variety of serious health problems," Chrousos said. "Anyone who suffers from chronic stress needs to take steps to alleviate it, either by learning simple techniques to relax and calm down, or with the help of qualified therapists.

About the authors

Melissa Braddock and Robert Bock are writers for the National Institute of Child Health and Human Development in Bethesda, Maryland. The article was developed with the cooperation of Dr Phillip Gold and the National Institute of Mental Health.

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223 NOVEMBER 2002 CATEGORY 1

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1. Which of the following is mismatched?
a. CRH: hypothalamus
b. ACTH: adrenal glands
c. epinephrine: increased blood pressure
d. cortisol: blood diverted to muscles

2. The limbic system in the brain controls ____.
a. motivation and mood
b. strength and agility
c. blood pressure and heart rate
d. none of the above

3. Genetic differences in the HPA axis could _____ to stress
a. prevent an appropriate response
b. cause and excessive response
c. both a and b
d. genetics don't affect the HPA axis

4. Which of the following hormone/responses are mismatched?
a. GnRH: reproduction
b. ACTH: digestion
c. IGF-1: growth
d. cortisol: immunity

5. In the reproductive system, stress affects _____.
a. ovulation
b. sperm release
c. testosterone levels
d. all of the above

6. Growth retarded fetuses have higher levels of which hormones?
a. ACTH, cortisol and CRH
b. cortisol & GnRH
c. IGF-1
d. IL-1 & IL-6

7. Which is an affect of stress on the gastrointestinal tract?
a. quickly emptying the colon
b. decreased stomach acid secretion
c. increased appetite
d. all are affected

8. Which is not an inflammation-causing substance?
a. IL-1
b. IL-6
c. IGF-1
d. TNF

9. Which of the following conditions are associated with high levels of CRH and cortisol?
a. malnutrition
b. hyperthyroidism
c. melancholic depression
d. all of the above

10. Which of the following conditions is not caused by an underactive stress system?
a. obsessive-compulsive disorder
b. Addison's disease
c. chronic fatigue
d. seasonal affective disorder

223 NOVEMBER 2002 CATEGORY 1

Chronic stress and stress disorders

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4	❑	❑	❑	❑	9	❑	❑	❑	❑
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