Sussing Out STRESS

Chronic stress makes people sick. But how? And how might we prevent those ill effects?

By Hermann Englert

Road rage, heart attacks, migraine headaches, stomach ulcers, irritable bowel syndrome, hair loss among women—stress is blamed for all those and many other ills. Nature provided our prehistoric ancestors with a tool to help them meet threats: a quick activation system that focused attention, quickened the heartbeat, dilated blood vessels and prepared muscles to fight or flee the bear stalking into their cave. But we, as modern people, are subjected to stress constantly from commuter traffic, deadlines, bills, angry bosses, irritable spouses, noise, as well as social pressure, physical sickness and mental challenges. Many organs in our bodies are consequently hit with a relentless barrage of alarm signals that can damage them and ruin our health.

Daily pressures raise our stress level, but our ancient stress reactions—fight or flight—do not help us survive this kind of tension.

What exactly happens in our brains and bodies when we are under stress? Which organs are activated? When do the alarms begin to cause critical problems? We are only now formulating a coherent model of how ongoing stress hurts us, yet in it we are finding possible clues to counteracting the attack.

The Road to Overload

In recent decades, researchers have identified many parts of the brain and body that contribute importantly to the stress reaction—the way we respond to external stressors. These regions process sensory and emotional information and communicate with a wide network of nerves, organs, blood vessels and muscles, reallocating the body's energy reserves so that we can assess and respond to situations.

When stress begins, a small area deep in the brain called the hypothalamus pulls the strings. It contains several different nuclei, or collections of neurons, that undertake various tasks. They regulate sleep and appetite, for example, and the balance among different hormones. The most critical collection of neurons is the paraventricular nucleus, which secretes corticotropin-releasing hormone (CRH), a messenger compound that unleashes the stress reaction.

CRH was discovered in 1981 by Wylie Vale and his colleagues at the Salk Institute for Biological Studies in San Diego and since then has been widely investigated. It controls the stress reaction in two ways.

Primarily, it reaches organs via the so-called long arm—the hormone signal pathway from the hypothalamus to the pituitary gland in the brain and to the adrenal glands on the kidneys. This long arm is also known as the hypothalamus-pituitary-adrenal axis.

When an emergency ends, the stress system must turn off so organs can recover. But constant anxiety keeps the system on, and organs never relax.

The arrival of CRH tells the pituitary to release adrenocorticotropic hormone (ACTH) into the bloodstream. ACTH, in turn, activates the adrenal glands to release glucocorticoid hormones into the blood. Levels of glucocorticoids typically follow a daily rhythm: high in the early morning, lower late in the day. One of their most important tasks is to increase glucose in the blood to provide energy for muscles and nerves. They also control glucose metabolism and the sleep-wake cycle. Because hormones regulate such critical functions, their levels have to be precisely controlled, and they are thus subject to a feedback mechanism in the hypothalamus, which can quickly return the system to lower values.

CRH also makes its effects felt by acting on the "short arm" pathway. A small region in the brain stem termed the locus coeruleus functions as a kind of neural relay station. It links the CRH-producing brain regions with the autonomic nervous system, which governs the ongoing physiological processes we never have to think about, such as breathing, blood pressure, digestion and so on.

The stress response system produces positive feedback to strengthen its own action when needed, but when daily stress builds up, it can become unnecessarily intense and sustained. Whether the response is appropriate or not depends on cells that coat the pituitary gland and other parts of the system. CRH sends signals into these cells by docking with type 1 receptor molecules on the cells' membranes. Researchers at the Salk Institute and at the Max Planck Institute of Psychiatry in Munich bred mice in which type 1 receptors were lacking. Even when these mice were repeatedly ex-

FAST FACTS

How Stress Harms the Body

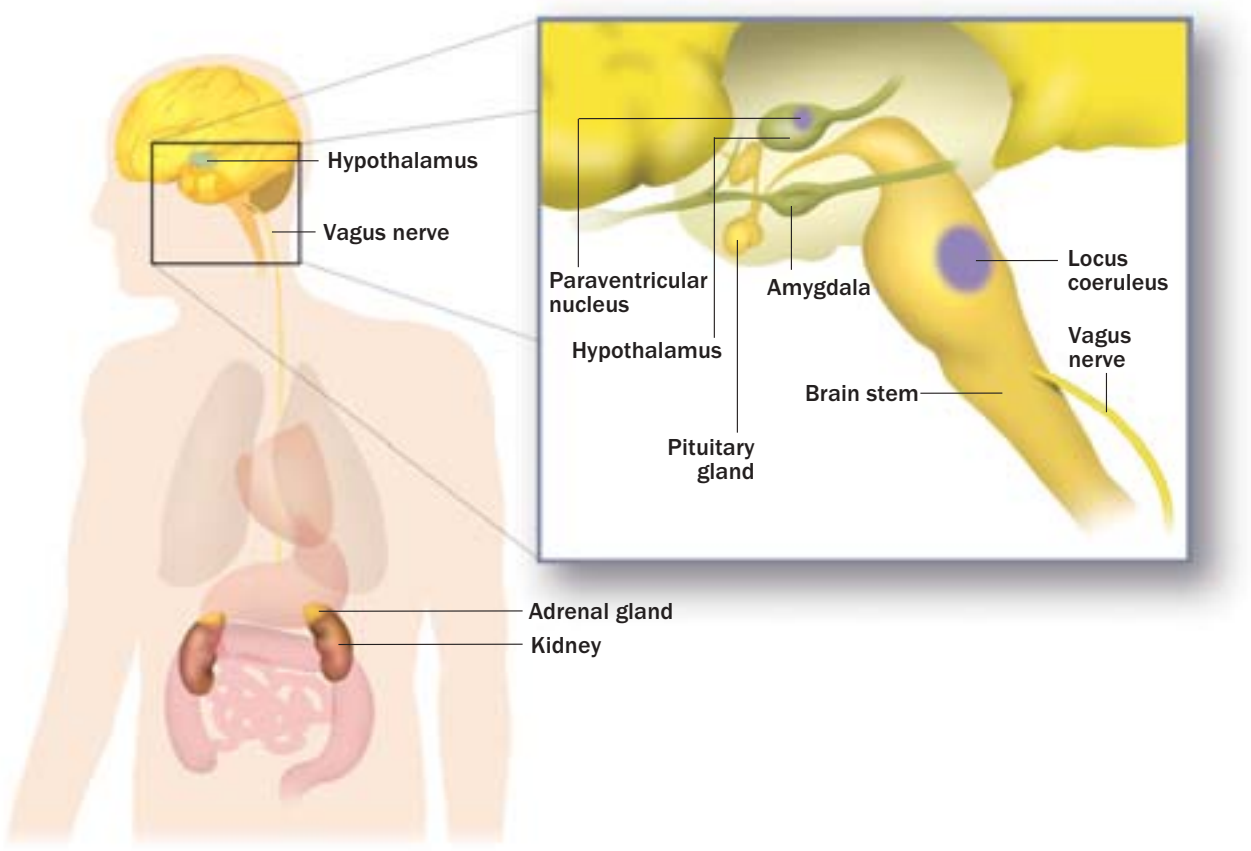
1» **Our stress system can quickly ramp up the heart, lungs and other organs so that we are ready to fight or flee sudden threats. But when we face unending stressors from modern life, the system can bombard our organs with relentless alarm signals that can wear down our organs and our health.**

2» **When vision, hearing or thoughts indicate "stress," the hypothalamus initiates a chain reaction involving the amygdala and the pituitary and adrenal glands, carried out by nerve impulses and a cascade of hormones, chief among them CRH, ACTH and glucocorticoids.**

3» **If researchers can determine exactly which receptor cells in the brain and glands propagate stress signals, they may be able to design drugs that can interfere, sparing organs the strain that stress creates.**

PHOTODISC/GETTY IMAGES (*preceding pages*)

Turning On



Stress signals change the physiological states of many organs, including the heart, kidneys, stomach and reproductive system, as well as muscles. The hypothalamus receives sensory stressors (such as seeing a bear) from nerves. The locus coeruleus (*blue spot*) delivers emotional stressors (such as worrying about the bear's teeth) from the amygdala to the paraventricular nucleus. That structure makes corticotropin-releasing hormone (CRH), the most important stress hormone, which tells the pituitary gland to send impulses via nerves such as the vagus and to release other hormones into the bloodstream. Those hormones activate the adrenal glands, which raise blood pressure and increase glucose levels in the blood, providing energy to fight or flee.

posed to stressful situations, levels of certain stress hormones in their blood never rose above normal. The animals obviously felt less stressed. Perhaps drugs that suppress the effects of CRH on these receptors might reduce stress levels in harried humans, too.

Organs Break Down

Our new knowledge of the stress system provides strong clues as to how stress can make us sick and how we might counteract its effects. For a mouse or human, any activation of the stress system counts as an extraordinary event—and when the emergency ends, the system must quickly be turned off so that the affected organs can recover. But when external circumstances stimulate the stress system repeatedly, it never stops reacting, and organs are never allowed to relax.

Such chronic strain leaves many tissues vulnerable to damage. The reproductive organs, for example, often become less effective. Research indicates that male and female athletes and ballet dancers who subject themselves to great physical demands over many years produce fewer sperm or egg cells. Male testosterone levels decline, and fe-

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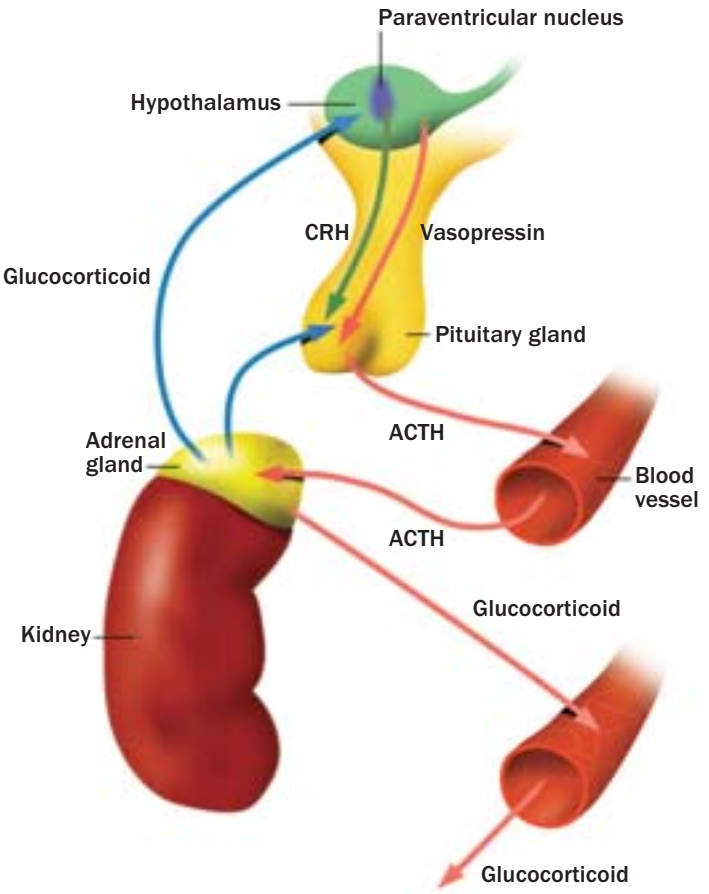
Tuning In



The hypothalamus runs the "long arm" of the stress system by secreting the hormone CRH. CRH flows through veins (*green arrow*) to the pituitary, which in turn releases the hormone ACTH into the blood. ACTH stimulates the adrenal glands to produce glucocorticoid hormones, which put the body on alert. In acute stress, the hypothalamus secretes vasopressin as well, to further activate the adrenals. The system regulates itself down after a threat is over via a negative feedback loop (*blue arrows*), in which glucocorticoids bathe both the hypothalamus to suppress CRH secretion and the pituitary to suppress ACTH. But daily stress may endlessly activate the system.

male menstrual cycles may become disordered or even cease.

Anorexia and long-term fasting have similar harmful effects on fertility. Both allow the level of CRH in the brain to increase. Anorexic patients have higher late-day levels of the stress hormone glucocorticoid cortisol in their plasma and urine than healthy people do. And when their pituitaries are artificially stimulated with CRH, anorexics secrete less of the hormone that mediates the stress response—evidence that their hypothalamus-pituitary-adrenal axis is hyperactive.

Excessive CRH from chronic stress also reduces the body's secretion of growth hormone, as well as its production of the substance that mediates the effects of growth hormone on organs. Children who are under great stress therefore grow more slowly. Among adults, the growth of muscles and bones and the metabolism of fat are hindered.

One of the most prevalent physiological effects of stress involves the stomach and intestines. When the hypothalamus-pituitary-adrenal axis is too active and levels of CRH in the brain are simultaneously too high, signals on the vagus nerve are blocked. This nerve, a major thoroughfare of the autonomic nervous system, controls contractions of the stomach and digestive tract. (It also sends nerve impulses to the heart and motor muscles.) A classic example of a stress-induced reaction by these organs is the shutdown of digestion after surgery. Some studies suggest that irritable bowel syndrome, a widespread complaint, is caused by too much CRH.

Other recent investigations find that victims of sexual assault or abuse, who almost always suffer some level of psychological damage even years after the abuse occurred, frequently also experience digestive disorders. In these same people, most of them young women, the hypothalamus-pituitary-adrenal axis is hyperactive. If it remains so for a long time, the metabolism of carbohydrates changes. Their body fat redistributes: fat deposits under the skin shift to the abdomen. Cells in their body may stop taking up the sugar glucose in response to insulin, a condition that can lead to diabetes in certain people.

An overactive hypothalamus-pituitary-adrenal axis can also cause symptoms that mirror those of mental illness. Indeed, the latest pharmacological research shows that too much CRH plays a role in mental disorders. Many depression patients, for example, have far too much cortisol in their blood. And the glucocorticoids in their blood are unable to suppress activity in the hypothalamus-pituitary-adrenal axis. In addition, they have too much CRH in their cerebrospinal fluid. Depressed people who commit suicide often have fewer CRH receptors in their brain's frontal cortex, an indication that, to defend itself against too much CRH, the brain reduces its susceptibility to the hormone.

The hypothalamus-pituitary-adrenal axis may also enhance phobias and panic attacks. [For more on the mental and physical processes of anxiety,

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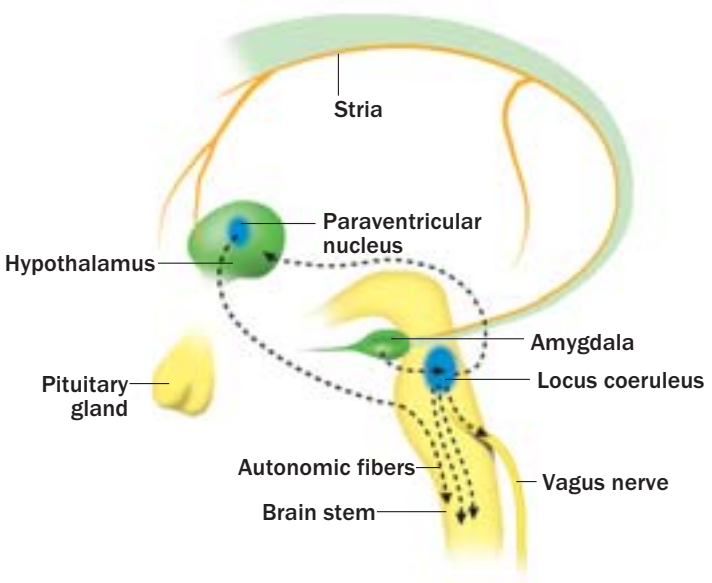
Stressing Out

A group of neurons in the brain stem, called the locus coeruleus, coordinates the "short arm" of the stress system along multiple nerve pathways (*black*). It signals the hypothalamus, which contacts autonomic nerve fibers in the brain stem. Other locus coeruleus neurons directly trigger stress responses in organs and glands through autonomic nerve fibers extending through the body. In sending its alerts, the locus coeruleus gets emotional inputs from the amygdala and the stria, which also reach the hypothalamus. Constant anxiety, frequent fear or aggression may cause nerves to fire unendingly, causing wear on the brain and body.



Drugs that suppress the reaction of receptor cells on the pituitary gland to the hormone CRH could reduce stress levels in harried humans.

see "Fear Not," on page 62.] Here again, too much CRH is present, causing the brain to be overactive. When CRH is injected into the brains of laboratory animals, they exhibit extreme fear. Patients with panic disorders such as agoraphobia (fear of open places) or claustrophobia (fear of confined spaces) secrete too little ACTH after they are given CRH as a drug. Clinical studies are under way in Europe to see whether patients with panic disorders can be helped by drugs that suppress the type 1 CRH receptors. Eventually, it is hoped, researchers will find ways to interrupt the overstimulated chain of command.

Measuring the Risk

Stress can make us sick, but not all stress is the same. A certain baseline level, called positive stress, is even desirable, because it keeps us mentally and physically ready to act and to perform well. But when are we at risk? There is no generally accepted answer to this question. We do not know how much workplace noise or how many broken relationships our stress systems can withstand. Yet an expanding portfolio of research shows that chronic stress is compromising our organs and bodies. Although we no longer face the bear in the cave, we may be in more dire straits, dealing with many more insidious stressors that are always tearing at us.

Before we can reduce this threat, we must learn how to measure each person's stress level. Physiologists are working on a set of parameters—such as CRH levels—that would be used to evaluate all the organs involved in the stress reaction. Once we know an individual is being harmed, then we must reduce the levels of stress he or she faces.

That, of course, may not always be possible in our complex world. So we must also develop therapies that prevent our stress system from ceaselessly racing. CRH, ACTH, their receptors and the hypothalamus-pituitary-adrenal axis are all possible targets. Researchers are busily investigating them—free, one hopes, of the stress that often accompanies important scientific pursuits.

(Further Reading)

- **A Chilled-Out Knockout.** Emiliana Borrelli in *Nature Genetics,* Vol. 19, No. 2, pages 108–109; June 1998.
- **The End of Stress as We Know It.** Bruce McEwen, with Elizabeth Norton Lasley. Joseph Henry Press, Washington, D.C., 2002.
- **Taming Stress.** Robert Sapolsky in *Scientific American,* Vol. 289, No. 3, pages 86–95; September 2003.

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