

# Evolutionary Origins and Functions of the Stress Response

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## Glossary

<i>Defense</i>	A trait that is latent until aroused by threatening situations in which it is useful.
<i>Natural selection</i>	The process by which genes that provide a fitness advantage become more common from generation to generation and those that decrease fitness become less common, thus shaping adaptive traits, including defenses.
<i>Phylogeny</i>	The evolutionary history of a trait or a species.
<i>Trade-offs</i>	The fitness costs and benefits of a trait whose net effects yield a selective advantage.

Evolution is the process in which traits such as the capacity for the stress response are shaped by natural selection. Understanding the evolutionary history of a trait, how it gives a selective advantage, and the costs it imposes can help to illuminate its design and regulation and can guide research into its mechanisms and control. The stress response has been shaped by natural selection to increase the ability of organisms to cope with situations that require action or defense. Stress-related mechanisms emerged early in the history of life. Like all traits, they have costs as well as benefits. Because the stress response is so often associated with negative events, its utility has often been neglected. In particular, the release of glucocorticoids, which is often thought to be the hallmark of the stress

response, may in fact exist, in part, to protect against other aspects of defensive systems.

## Utility of the Stress Response

The vast bulk of research on stress has investigated its causes, mechanisms, and effects. An evolutionary approach instead addresses two very different and relatively neglected questions: (1) How does the stress system give a selective advantage and (2) what is the evolutionary history of the stress system? The answers to these questions provide a foundation in Darwinian medicine for understanding why the stress response is the way it is and why it causes so much suffering and disease. The first and most important contribution of an evolutionary perspective on stress is a clear focus on its utility. The stress system is a complex, sophisticated, and carefully regulated adaptation that has been shaped by natural selection because it gives a selective advantage. That advantage must be substantial in order to outweigh its huge costs. The idea that stress is useful is by no means new. In fact, the very phrase Hans Selye chose to describe it, the general adaptation syndrome, emphasizes its utility. Despite this early emphasis on its benefits, as the idea of stress entered the popular imagination there was a tendency to emphasize its dangers so that the fundamental fact of the utility of the stress response was often forgotten.

## Stress and Other Defenses

Other defenses are also often confused with the problems they protect against. The capacities for pain, fever, vomiting, cough, and inflammation are often thought of as medical problems, although a moment's thought reveals that they are useful protective reactions. The ubiquity of the illusion that defenses are abnormalities arises from several sources. First, defenses are often associated with some kind of suffering and therefore seem maladaptive. Unfortunately, however, discomfort is itself probably one aspect of a mechanism that makes it useful. Second, they are reliably associated with disadvantageous situations, so the association bias makes it seem as if they are the problem. Finally, it is possible to use drugs to block the expression of many defenses with very little harm, completing the illusion that defenses are useless. In fact, blocking

a defense can be harmful. For instance, suppressing cough in a patient with pneumonia makes it harder to clear the infection and may lead to death, and stopping the diarrhea of a person with a serious intestinal infection may lead to complications. Blocking fever, however, usually has little effect on the speed of recovery from a cold. When blocking a defense is not dangerous, this is because the body has backup protective mechanisms and because the regulation mechanism seems to be set to a hair trigger that expresses the defense at the slightest hint of danger.

### **Situations in Which Stress Is Useful**

Stress, like fever and pain, is useful only in certain situations. Such traits lie latent until aroused by the particular circumstances in which they are useful. This means that the evolutionary explanation for such traits cannot be summarized in a single function. Instead, the inducible defenses give an advantage by changing multiple aspects of the body that increase its ability to cope effectively with the adaptive challenges that arise in a particular situation. One defense may have many aspects that serve many functions. So, the first step in understanding the adaptive value of stress is not to try to specify its function but to understand the exact situations in which the stress response is useful. To do that, we need to go back to the very origins of complex life forms 600 million years ago. If a very primitive organism had only two states, what are they? The answer is quite straightforward: activity and rest. This is a fundamental divide, one that is maintained even in our biochemical and nervous systems. Biochemical pathways are divided into the catabolic, in which energy is used, and the anabolic, in which energy is stored and tissues are repaired. Parallel to this division are the two arms of the autonomic nervous system. The sympathetic system, which is activated as part of the stress response, increases arousal, blood pressure, heart rate, respiratory rate, and physical activity and institutes other endocrine and physiological changes necessary for action. The other half of the autonomic nervous system, the parasympathetic, inhibits muscular activity, stores energy, and shunts blood to digestion and bodily repair. Is stress, then, the same as arousal for action? Not exactly. As soon as a generic state of arousal was well established, natural selection probably began to differentiate it into subtypes to better meet the demands of different kinds of challenges. Here again, the main bifurcation is quite clear. Arousal is useful in two different situations: threats and opportunities. This division is also represented in our nervous systems. As Gray and others have pointed out, the brain seems to have moderately distinct systems for behavioral inhibition and for reward

seeking. The corresponding behaviors are said to be defensive or appetitive and are associated with feelings of fear/pain or pleasure. In psychology, the same division is recognized in the distinct cognitive states promotion versus prevention.

## **Phylogeny of the Stress Response**

### **Cross-Species Comparisons**

Comparisons among different species can help to reconstruct the phylogeny of the stress response. All vertebrates have the proopiomelanocortin (POMC) molecule that gives rise not only to adrenocorticotrophic hormone (ACTH) but also to opiate-like peptides. It is intriguing to note that these molecules, with their related functions, are derived from the same parent molecule. All vertebrates also make corticosteroids. Peptide sequences very similar to those of human ACTH are found not only in mammals but also in amphibians and reptiles and even in insects, mollusks, and marine worms. Interestingly they are usually associated with immune cells, equivalent to macrophages, where they set defensive processes in motion. ACTH has long been closely associated with other signaling molecules such as corticotropin releasing hormone (CRH), biogenic amines such as epinephrine and norepinephrine, steroids such as cortisol, cytokines such as interleukin-1, and nitric oxide. All these substances are crucial to defensive systems. The remarkable thing is that genetic sequences for these molecules have not only been conserved over hundreds of millions of years but they continue to serve closely related defensive functions. Why have they changed so little? If a single molecule has several essential functions, this creates a strong selective force against mutations that change the sequence. By contrast, mutations that result in the differentiation of different classes of receptors in target tissues can slowly specialize the responses of that tissue to the signal molecule. And they have, judging from the proliferating classes and subclasses of receptors that are now being discovered.

### **Cost-Benefit Trade-Offs**

Why is the stress system not better? It could provide more effective protection against danger – but only at a still greater cost. *Drosophila* have been bred to resist the stress of food shortage. After 60 generations of such selection, the new strain is 80% more resistant to starvation. However, the larvae are more likely to die, and development is slowed. Similar results have been found for selection of resistance to other stressors and in other species. Like everything else in the body, stress responses are shaped by trade-offs, some-

times with benefits and costs occurring in different parts of the life cycle.

The mechanisms that regulate the responsiveness of the stress system are shaped by the trade-off between the long-term costs and the immediate benefits of a relatively quick or intense or prolonged stress response. It has been hypothesized that the individuals who are most resilient or resistant to the effects of stress on physiology or behavior are the ones least vulnerable to stress-related diseases. However, are these individuals resilient to all stress-related disorders, or are there situations in which resilience to some disorders means vulnerability to others? The answer is not known, but given the large number of physiological systems affected by stress and/or glucocorticoids, it is unlikely that resilience to one stress-related disorder necessarily protects against all.

Another trade-off reflects the benefits and costs of habituation. For instance, rats exposed to some repeated stressors, particularly those that are mild and cognitive in nature, habituate to that stressor. The hypothalamic-pituitary-adrenal (HPA) response is lower to the  $n$ th exposure than to the first exposure. Such habituation seems adaptive for most situations; if the stressor is known and can be easily coped with, then the HPA response should be moderated. Such habituation would, at the very least, conserve resources. However, it would be maladaptive to habituate to stressors that do present some danger. These trade-offs have shaped the brain mechanisms that regulate habituation.

There are interesting sex differences in the habituation of the stress response, with some evidence indicating that habituation occurs in male but not in female rats. Such findings suggest that the selection forces acting on male and female rats may have differed enough to shape distinctly different patterns of habituation. Research is now addressing whether habituation occurs with some stressors in males but with others in females.

Stress responses in adult animals are profoundly affected by early environmental events such as prenatal stress and variations in maternal care. The effects of variations in maternal care are transmitted across generations, with offspring that experience high maternal care exhibiting lower stress responses and providing high maternal care themselves. Such effects seem adaptive in that offspring are likely to experience an environment similar to that of their parents. So, for example, mothers providing low maternal care have high stress responses and so do their offspring when they become adults. However, when cross-fostered to other mothers, the offspring show patterns of stress responsivity similar to that of their foster mother and not their biological mother. Such

results suggest that stress responsivity and maternal care are not simply genetically transmitted but are also regulated by early experiences. Such regulation is seen in other mammals and even plants. Some of such transmission across generations may arise from facultative mechanisms that evolved to adjust the system based on early life experiences, and some may arise from more general learning mechanisms.

### Difficulties in Defining Stress

The human mind seems wired to try to make neat categories with sharp boundaries, perhaps because we communicate with words and this requires dividing the world up into categories even when that is unnatural. This leads to a tendency to try to make sharp distinctions between different states that may, in fact, overlap considerably. States of defensive arousal, for instance, are different from states of arousal for seeking food, but there is no reason to expect that the differentiation is complete. For instance, cortisol secretion is aroused by opportunities as well as threats. In fact, cortisol is even involved in reward mechanisms. Thus, any attempt to define the stress response in terms of cortisol arousal is doomed. For that matter, any attempt to define stress or the stress response is liable to be an exercise in frustration for the evolutionary reason that the system does not have sharp boundaries or a single function. The closest we can come to a defining characteristic is the kinds of situations in which stress has given a selective advantage, and those situations are not sharply defined. The stress system was, after all, not designed by an engineer but shaped by a process of tiny tinkering changes. The long unsatisfying history of attempts to define stress and the wish, expressed by many researchers, that the term would go away, arise from this difficulty. Even after defensive arousal was differentiated considerably from appetitive arousal, there were undoubtedly advantages to further differentiating subtypes of stress responses to match specific challenges. Thus, different situations – a predator, a high place, injury, infection, starvation, loss of a status battle, and speaking in public – all seem to have shaped somewhat different defensive responses. These responses are only partially differentiated from a more generic response, so they have overlapping characteristics with functions in common. Attempts to sharply distinguish different kinds of anxiety disorders are as frustrating as attempts to define stress itself and for the same reasons. New attempts to study anxiety disorders in the context of normal anxiety will be helpful.

## **How Does the Stress Response Help?**

### **Immediate Response**

These difficulties notwithstanding, a stress response is a coordinated pattern of changes that is useful in situations in which the organism is faced with possible damage or a loss of resources. The next question is: How is it useful? Even before Selye, Walter Cannon provided some answers. In situations that might require fight or flight, he observed the utility of increased heart rate and contractility to speed circulation, increased rate and depth of breathing to speed gas exchange, sweating to cool the body and make it slippery, increased glucose synthesis to provide energy, shunting of blood from gut and skin to muscles, increased muscle tension to increase strength and endurance, and increased blood clotting in preparation for possible tissue damage. More recently, others have demonstrated faster reaction times and cognitive benefits as a result of sympathetic arousal. These immediate responses are mostly mediated by the sympathetic nervous system and the associated release of epinephrine from the adrenal medulla.

### **Adrenal Cortical Response**

However, the stress system also includes a more delayed-response release of cortisol from the adrenal cortex, although this system does have more rapid effects (such as fast negative feedback) that are probably mediated by putative membrane steroid receptors. This is initiated by neural signals to the hypothalamus, which releases CRH, which in turn results in the secretion of ACTH from the anterior pituitary gland on the bottom of the brain. The ACTH induces cortisol synthesis and release from the adrenal gland. The whole system is called the HPA system because the signal acts via the hypothalamus, the pituitary, and the adrenal glands. Many actions of the HPA system seem, like those of the sympathetic system, well designed for acute action. It changes physiology so the liver breaks down glycogen into glucose, and it alters cells so glucose can get in more readily. Through different populations, CRH not only releases ACTH, but it also directly increases anxiety and arousal and activates cells in the locus coeruleus, the brain center where the cell bodies for most noradrenergic neurons are located. All in all, the system seems admirably designed to get the organism ready for action. Indeed, both branches of the system are readily aroused by exercise, and trained athletes, far from having low levels of cortisol, have chronic high levels – just the thing for a person who frequently exerts him- or herself.

### **Association with Negative Events**

So, why should the stress system as a whole be associated so closely with bad events instead of positive ones? To answer that question, we need to understand why the components of the stress system are carefully packaged. If the stress is so useful, why is stress not expressed all the time? There are at least three good reasons why it is not. First, it is expensive in terms of calories. No organism can afford to waste effort. Second, it interferes with other adaptive behaviors. A vigilant organism has less time for finding food and eating, to say nothing of mating. Finally, and most important, some changes that give an advantage in the face of threats may also cause tissue damage. For this reason, they need to be carefully sequestered, except in those few circumstances in which the costs are outweighed by the benefits. This helps to explain why some aspects of the stress response are associated more with negative than positive arousal. The benefits of a stress response that increases the likelihood of catching prey may sometimes be worth it, but if a stress response prevents being caught as prey, this is always worth it, even if substantial damage results from the stress response itself. This helps to explain why the stress response, despite its costs, is so ubiquitous. An optimal regulatory mechanism will express a stress response whenever, on average, it is worth it. Given the uncertainties of environmental cues and the potential life-saving effects of the stress response, there will be many instances where the expression of stress is worthwhile, even though there is only a small chance that danger is actually present. The global conclusion is that the damage caused by stress responses is not necessarily from abnormal stress. Some components of the stress response may be a part of the response specifically because they are too damaging to be expressed except when they protect against great danger. There is every reason to think that normal stress, like every other bodily trait, has costs as well as benefits. This idea is expressed in the concept of allostasis, as proposed by McEwen and colleagues, which emphasizes the short-term benefits and the long-term costs.

That a normal stress response might be crucial for optimal physiological functioning has implications for recent notions about pharmacological therapies for reducing perceived stress. For example, if a drug such as a CRH inhibitor blocks all stress response at the brain level, then how does the body react to what may be real requirements for increases in energy use and how do systems that are generally opposed in functions to those of glucocorticoids, counterregulatory systems such as the regulation of insulin release, stay in check? Furthermore, there are many indica-

tions in both human and animal studies of mismatches between perceived stress or behavioral indices of stress and HPA activation. The extreme of an absent stress response is, of course, Addison's disease. Thus, although the cognitive nature of many current human stressors results in costs disproportionate to actual threats, from an evolutionary point of view the general inhibition of stress responses is by no means optimal. It would be ironic as well as tragic if the history of the excessive use of cortisone were to repeat itself with a new generation of drugs that block the stress response.

### **Cortisol as Protection against Other Aspects of Stress**

If some aspects of the stress response cause harm, has selection shaped systems to protect against this damage? In 1984, Munck and colleagues reviewed the actions of cortisol and said, "We propose that stress-induced increases in glucocorticoids levels protect, not against the source of stress itself, but rather against the body's normal reactions to stress, preventing those reactions from overshooting and themselves threatening homeostasis." They noted that many inflammatory diseases had been attributed to overproduction of cortisol until 1941, when adrenal steroids were shown to decrease inflammation. Subsequent demonstrations showed that steroids inhibit the production of cytokines, prostaglandins, and other mediators of the immune response, thus decreasing immune function. This is just the opposite of what would make sense as protection from danger, but it is entirely consistent with a role in protecting against damage from immune system activation induced by other changes. It is now clear that the effects of glucocorticoids on immune function are much more complicated than originally thought. Added to this are recent novel findings regarding the effects of glucocorticoids on the brain versus the body on the regulation of energy balance and fat deposition that suggest that our assumptions about the physiological and neural functions of glucocorticoids will continue to be significantly challenged.

### **Adaptive Regulation of Stress Responsiveness**

The recognition that a moderately responsive stress system is optimal is quickly leading to a consideration of the adaptive significance of variations in stress responsiveness. Several lines of thinking addresses the adaptive significance of innate individual differences in stress responsiveness. The first attempts to explain the growing evidence for a bimodal pattern

of stress response in some organisms, with some individuals responding quickly and strongly and others showing a much more restrained response. It has been suggested that these distinct patterns reflect distinct patterns of adaptation; a hawk pattern that is optimal in crowded situations and a dove pattern that is optimal when population density is low. The different strategies are hypothesized to be the products of frequency-dependent selection. There is also increasing evidence that maternal effects on an offspring's stress responsiveness may be adaptive. Mothers exposed to stressful environments give birth to offspring with especially responsive stress systems that may give them an advantage in harsh environments. The same evolutionary forces may have shaped mechanisms that explain the connection between early abuse or neglect and increased stress vulnerability.

### **Mismatch between Ancestral and Modern Environments**

Much has been made of the differences between our environment and that of our ancestors. In the case of stress, this argument comes in several flavors. Some suggest that life is more stressful now than it was for our predecessors. Special aspects of our environment do cause new kinds of stress. Working in a bureaucracy is tedious and political at best. Driving to work, living in a ghetto, running a corporation, working in a factory – these all arouse the stress system. Despite the amount of stress we experience, however, our ancestors almost certainly experienced more. With no police, no food reserves, no medicine, no laws, rampant infections, and prevalent predators, danger could come at any time. True, social groups were closer, kin networks were stronger, and people spent all their time with one another and none alone reading books. Still, life was hard. Perhaps in that environment, where stressors were more often physical, the stress response was more useful than it is now. Today, we mainly face social and mental threats, so the actions of the HPA system may yield net costs. This is plausible and supports the many efforts to reduce stress and to find drugs that block the stress response. This brings us back to the very concept of stress as a mismatch between the demands made on an individual and that individual's ability to meet those demands. We think of these demands as coming from the outside, and sometimes they do, as when we are attacked by the proverbial tiger. But most stresses in modern life arise not from physical dangers or deficiencies but from our tendency to commit ourselves to personal goals that are too many and too high and to ruminate about them. When our efforts

to accomplish these goals are thwarted or when we cannot pursue all the goals at once and must give something up, the stress reaction is expressed. In short, much stress arises, ultimately, not from a mismatch between our abilities and the environment's demands, but from a mismatch between what we desire and what we can have.

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## Excitatory Amino Acids

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Synthesis and Release  
Glutamate Receptors  
Termination of Action  
Excitotoxicity

### Glossary

<i>Excitatory postsynaptic potential (EPSP)</i>	The electrophysiological response evoked by glutamate released from mammalian nerve terminals.
<i>Excitotoxicity</i>	Cellular injury caused by compounds, such as glutamate, that are both neuroexcitatory and neurotoxic.
<i>Inotropic receptor</i>	An ion channel with binding affinity for a particular ligand, in which ligand binding promotes channel opening.
<i>Long-term depression</i>	A long-lasting, stable reduction in the size of the postsynaptic response.
<i>Long-term potentiation</i>	A long-lasting, stable increase in the size of the postsynaptic response.
<i>Metabotropic receptor</i>	A macromolecule with binding affinity for a particular ligand, in which ligand binding produces a physiological effect