CHAPTER

11

Evolutionary Origins and Functions of the Stress Response System

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OUTLINE

Abstract

Evolution is the process in which traits such as physiological stress response systems (SRSs) are shaped by natural selection. A full understanding of any trait requires knowing its evolutionary history, how it has given a selective advantage, and the trade-offs and costs involved. 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. This chapter reviews the phylogeny and functional significance of the SRS, with a special focus on how selection has shaped the mechanisms that process environmental information to regulate the stress response, and how the stress response influences other traits such as risk-taking and sexual behavior.

UTILITY OF THE STRESS RESPONSE SYSTEM

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 response system (SRS) give a selective advantage? and (2) What is the evolutionary history of the SRS? The answers to these questions provide a foundation in Darwinian medicine[1] 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 SRS is a complex, sophisticated, and carefully regulated adaptation that has been shaped by natural selection because its advantages that must be substantial in order to outweigh its huge costs.[2] 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.[3] Despite this early emphasis on its benefits, as the idea of "stress" has entered the popular imagination, there has been a tendency to emphasize its dangers so that the fundamental fact of the utility of the stress response is often neglected.

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KEY POINTS

- The stress response system was shaped by natural selection to adjust physiology and behavior to changing circumstances, especially regarding energy usage and environmental threats and opportunities.
- Selection shaped the stress regulation system to express the stress response whenever the benefits are greater than the costs.
- In many situations, the costs of expressing a stress response are low compared to the costs of not expressing the response if a major threat is present, so false alarms are expected in the normal system (the "smoke detector principle").
- Selection has shaped mechanisms that adjust the threshold and magnitude of stress responses as a function of prior experience.

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, defenses are reliably associated with disadvantageous situations, so the association bias makes it seem as if they are the problem. Finally, it is often possible to use drugs to block the expression of many defenses with very little harm, fostering the illusion that defenses are useless. In fact, blocking a defense can be harmful. For instance, suppressing cough for a patient with pneumonia makes it harder to clear the infection and may lead to death. 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 back-up protective mechanisms and because the regulation mechanism seems to be set, for reasons we revisit, to a hair-trigger that expresses the defense at the slightest hint of threat.[4]

Situations in which Stress is Useful

Stress responses, like fever and pain, are useful only in certain situations. These responses have low basal activation levels 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, inducible defenses give advantages by changing multiple aspects of the body that increase its ability to cope effectively with the adaptive challenges that arise in a particular kind of 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 specify its function, but to understand the situations in which the stress response is useful.

To do that, we need to go back to the origins of complex life forms 600 million years ago. If a very primitive organism had only two states, what would they be? 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 established, natural selection likely began to differentiate it into subtypes to better meet different kinds of challenges. Here again, the main bifurcation is 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.[5] 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 described by "promotion" as compared to "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 molecule that gives rise not only to adrenocorticotropic 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, reptiles, and even in insects, mollusks, and marine worms. Interestingly, these peptides 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 CRH (corticotrophin releasing hormone), biogenic amines such as epinephrine and norepinephrine, steroids such as cortisol, cytokines such as interleukin-1, and nitric oxide. All 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 will create a strong selective force against mutations that change the sequence. By contrast, mutations that result in 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 isn't the SRS better? It could provide more effective protection against danger, but only at a still greater cost. Soldiers undergoing high-intensity military survival training show increases in the sympathetic neural transmitter neuropeptide Y (NPY) following interrogations.[6] This increase plays a functional role in adjusting to high-stress conditions: soldiers who experienced greater increases in NPY remained more interactive with their environment and were rated as exhibiting greater mental alertness during the interrogations.[6] The trade-off is that up-regulation of the NPY system mediates stress-induced obesity and metabolic syndrome.[7] Like everything else in the body, stress responses are shaped by trade-offs, sometimes with benefits and costs occurring in different parts of the life cycle.

The mechanisms that regulate the responsiveness of the SRS are shaped by the trade-off between the long-term costs versus the immediate benefits. Individuals who have smaller stress responses may be less vulnerable to stress-related diseases,[8] but they may be less able to cope with some stressors. The SRS responds not only to threats and challenges, but also to novel stimuli and positive social opportunities (e.g., unexpected or exciting rewards, opportunities for status enhancement, potential sexual partners). For example, in a naturalistic study on a Caribbean island, significantly elevated cortisol levels among children were documented during the 2 days prior to Christmas, compared with a control period, but only among children who had high expectations for presents or other exciting activities.[9] More generally, the SRS appears to mediate the effects of environmental influences, operating as an amplifier (when highly responsive) or filter (when unresponsive).[10] This dual function of the SRS is captured by the concept of *biological sensitivity to context*.[11] Lack of response to adversity and stress-related disorders may be associated with inability to take advantage of opportunities.

Resilience is a dynamic concept[12,13] that to some extent must be environment and stressor specific. An individual resilient to one type of stressor may be vulnerable to another. More interestingly, a response profile that was resilient in one environmental context may now produce vulnerability because the response profile is optimal for another environment.[14] Thus, systems that adjust the responsiveness of the SRS give a selective advantage.

Other trade-offs reflects the benefits and costs of habituation (down-regulation) and sensitization/facilitation (up-regulation) of SRS parameters.[15] For instance, rats habituate to mild cognitive stressors.[16] Habituation conserves energy when the stressor is known and can be easily coped with. However, habituation to unpredictable dangerous situations can be maladaptive, so sensitization may be useful, despite the risks of positive feedback dysregulation. These trade-offs have shaped the brain mechanisms that regulate the SRS.

In the longer term, activation of autonomic, neuroendocrine, metabolic, and immune system responses during ontogeny provides information about threats and opportunities likely to be encountered throughout life. Over time, this information becomes embedded in set points and reactivity patterns of an individual's SRS.[2] Thus, understanding the long-term impact of stress during development requires attention to the changes in an individual's environment from adolescence to adulthood. The impact of a specific kind of stress on SRS regulation mechanisms during development may be advantageous when the environment stays the same, but disadvantageous if the environment shifts.[14,17] Mismatch between early life experience and the adult environment may cause excessive or deficient responses to stressors experienced later in life.

Habituation and sensitization of the SRS is different for the sexes in rats, with males showing greater tendencies to habituation.[18] Selection forces acting on males and females may have differed enough to shape different patterns of habituation, a topic of current research. Humans show consistent sex differences in the type of events that elicit a SRS response and in the physiological and behavioral correlates of the response. Men tend to show more hypothalamic-pituitary-adrenal (HPA) activation than women in achievement-related tasks (which may elicit status-related motives), whereas women show

larger HPA activation in situations involving social rejection.[19]

Stress responses in adult animals are profoundly affected by prenatal stress and variations in maternal care. The effects of variations in maternal care are transmitted across generations with offspring who experience high maternal care exhibiting lower stress responses and providing high maternal care themselves.[20] Such effects would be adaptive when offspring experience an environment similar to their parents. Mothers providing low maternal care tend to have high-stress responsiveness, as do their offspring when they become adults. However, offspring cross-fostered to other mothers show patterns of stress responsivity more similar to that of their foster mothers. Such results suggest that stress responsivity and maternal care are influenced by early experiences as well as genetic factors. Such regulation is seen in other mammals and even plants.[20] Some transmission across generations may be mediated by facultative epigenetic 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 this differentiation is not 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 SRS in terms of cortisol arousal is doomed. For that matter, any attempt to define stress or the SRS 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 responses have given a selective advantage, and those situations are not sharply defined. The SRS 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 from 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.[21] These responses are only partially differentiated from a more generic response so they have overlapping characteristics with functions in common. For the same reasons, attempts to sharply distinguish different kinds of anxiety disorders are as frustrating as attempts to define stress itself. New attempts to study anxiety disorders in the context of normal anxiety will be helpful.

HOW DOES THE SRS HELP?

Immediate Response

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/gain 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.[22] 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

The SRS also includes release of cortisol from the adrenal cortex, a more delayed response, although one with some rapid effects such as fast negative feedback that are likely mediated by putative membrane steroid receptors.[23] Cortisol release is initiated by neural signals to the hypothalamus that releases CRH, which in turn results in secretion of ACTH from the anterior pituitary gland. 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 glycogen down into glucose, and it increases the entry of glucose into cells.[24] CRH not only releases ACTH, 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, as is appropriate to cope with high levels of exertion.

Association with Negative Events

So, why should the SRS 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 SRS are carefully packaged. If stress responses are so useful, why aren't stress responses expressed all the time? There are at least three good reasons. First, it is calorically expensive. No organism can afford to waste energy. Second, it interferes with other adaptive behavior. A vigilant organism has less time for finding food and eating, to say nothing of mating. Finally, some changes that give an advantage in the face of threats also cause tissue damage. For this reason, they need to be carefully sequestered, except in circumstances in which the costs are outweighed by the benefits. This helps to explain why some aspects of the SRS 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 the costs, but a response that prevents being caught, as prey will almost always be worth almost any costs. An optimal regulatory mechanism will express a stress response whenever, on average, the benefits are greater than the costs. This "smoke detector principle," based on a signal detection analysis of how selection shapes mechanisms that regulate defense responses explains why so many instances of stress response seem excessive or unnecessary.[4] The global conclusion is that the damage caused by stress responses is not necessarily from "abnormal" stress. Some components of the SRS may be a part of the response specifically because they are too damaging to be expressed except when they protect against great danger. Normal stress, like every other bodily trait, has costs as well as benefits. This idea is expressed in the concepts of allostasis and allostatic load, as proposed by McEwen,[25] which emphasizes the short-term benefits and the long-term costs.

The idea that the normal stress response is crucial for optimal functioning has implications for proposed pharmacological therapies for reducing stress responses. For example, a CRH inhibitor that blocks stress responses can be expected to disrupt the body's adaption to situations that call for increased energy use. Disrupting the normal operation of the HPA system is also likely to interfere with counter-regulatory systems, such as regulation of insulin release. Furthermore, human and animal studies provide many examples of mismatches between perceived stress and 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, general inhibition of stress responses is by no means optimal. It would be an irony as well as a tragedy if the history of excessive use of cortisone were to repeat itself with a new generation of drugs that block the SRS.

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."[26] 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 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 is entirely consistent with a role in protecting against damage from immune system activation induced by other SRS induced changes. The effects of glucocorticoids on immune function are much more complicated than originally thought. For instance, recent findings regarding the effects of glucocorticoids on the brain versus the body on regulation of energy balance and fat deposition[27] suggest continuing challenges to our assumptions about the physiological and neural functions of glucocorticoids.

ADAPTIVE REGULATION OF STRESS RESPONSIVENESS

The bimodal pattern of stress response in some organisms, with some individuals responding far more quickly and strongly than others, may result from frequency dependent selection for fast response "hawk" patterns that are optimal in crowded situations, while a "dove"

pattern is otherwise better.[28] Maternal effects on an offspring's stress responsiveness may also be adaptive. Mothers exposed to stressful environments give birth to offspring with especially responsive stress systems that may give an advantage in harsh environments,[20] a finding that may help explain the connection between early abuse and increased stress vulnerability.

Several other lines of thinking also address the adaptive significance of individual differences in SRS functioning.[29] Integrating and extending these past theories, the Adaptive Calibration Model is an evolutionary theory of developmental programing focusing on calibration of SRSs and associated life history strategies to local environmental conditions. It attempts to move beyond the primarily descriptive science that now dominates SRS studies to more explanatory models that seek to account for individual differences and their adaptive significance. For example, exposures to danger, unpredictable or uncontrollable contexts, and social evaluation generate sustained activation of the HPA axis.[30] Because HPA responses track the key environmental variables, they can feed into mechanisms that adjust life history strategies via changes in defensive behaviors, competitive risk-taking, learning, attachment, affiliation, and reproduction.[31]

MISMATCH BETWEEN ANCESTRAL AND MODERN ENVIRONMENTS

Much has been made of the differences between our environment and that of our ancestors.[32] 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 SRS. 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 each other, none of it alone reading books. Still, life was hard. Perhaps in that environment, where stressors were more often physical, the SRS was more useful than it is now. Today, we mainly face social and mental threats, so the actions of the HPA system may more often yield net costs. This plausible hypothesis supports efforts to reduce stress and to find drugs that block the SRS.

This brings us back to the general concept of stress as aroused when demands are greater than an individual's ability to meet them. 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 why we cannot achieve them all. 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 SRS is activated. 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.

Glossary

Defense A trait that is latent until aroused by threatening situations in which it is useful.

Evolutionary medicine The application of evolutionary biology to address problems in medicine and public health.

Natural selection The process by which genes that give a fitness advantage become more common from generation to generation and those that decrease fitness become less common, thus shaping adaptive traits, including defenses.

Phylogeny The evolutionary history of a trait or a species.

Trade-offs The fitness costs and benefits of a trait whose net effects yield a selective advantage.

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