during times of stress. It is important for researchers to study the conditions under which different types of support are beneficial or harmful.

Overmier and Murison review animal studies that document the effects of psychological states such as stress on the development of peptic ulcers. Animal models of research are important to health psychology because they allow researchers to conduct more tightly controlled experiments that are often not feasible and/or ethical in human subjects. For example, researchers have exposed animals to chronic stressors such as shock, and by doing so have been able to convincingly demonstrate that stress leads to the development of ulcers. This work also has revealed that the stress responses can be modulated—for example, allowing animals to predict when the stressor will occur or to control the stressor will reduce the likelihood of ulcer. Importantly, Overmier and Murison discuss the notion that stress is not the sole cause of ulcers, but rather that it modifies other processes, such as animal's ability to fight off the bacteria that cause disease. Thus, it is critical for researchers to understand how psychosocial characteristics interact with microbial organisms and biological systems involved in defense.

The last two articles discuss the specific roles of the immune system and genes in the relationship between social/environmental factors and disease. Ader emphasizes how the immune system is not autonomous, but is affected by other biological systems, as well as behavior. Ader demonstrates how the immune system can be modified by external stimuli—for example, animals can be conditioned to exhibit an immune response when they are exposed to a stimulus that has nothing to do with the immune system (e.g., a sweet liquid), if that stimulus has previously been paired with a drug that affects the immune system. Gottlieb discusses how genes and environment affect behavior, and dispels the myth that genes work unidirectionally to influence behavior. Instead, Gottlieb presents evidence that genes themselves are affected by environmental stimuli. This implies that we should not be thinking that genes are determining our destiny, but rather of genes and environment as working together and influencing each other to shape human behavior. This will likely be one of the most important next frontiers in research on mechanisms in health psychology—determining how psychosocial and environmental characteristics influence the turning on and off of genes.

The Psychobiology of Stress

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Abstract

Stressful life experience can have significant effects on a variety of physiological systems, including the autonomic nervous system, the hypothalamic-pituitary-adrenal axis, and the immune system. These relationships can be bidirectional; for example, immune cell products can act on the brain, altering mood and cognition, potentially contributing to depression. Although acute physiological alterations may be adaptive in the short term, chronic or repeated provocation can result in damage to health. The central dogma in the field of stress research assumes a stereotyped physiological response to all stressors (the generality model). However, increasing evidence suggests that specific stressful conditions and the specific way an organism appraises these conditions can elicit qualitatively distinct emotional and physiological responses (the integrated specificity model). For example, appraisals of threat (vs. challenge), uncontrollability, and negative social evaluation have been shown to provoke specific psychobiological responses. Emotional responses appear to have specific neural substrates, which can result in differentiated alterations in peripheral physiological systems, so that it is incorrect to presume a uniform stress response.

Keywords

stress; endocrine; autonomic; immune; physiology; emotion; cognitive

The term stress is used in the scientific literature in a vague and inconsistent way and is rarely defined. The term may refer to a stimulus, a response to a stimulus, or the physiological consequences of that response. Given this inconsistency, in this review I avoid using the term stress (except when discussing the field of stress research) and instead differentiate the various components of stress. *Stressors*, or stressful life experiences, are defined as circumstances that threaten a major goal, including the maintenance of one's physical integrity (physical stressors) or one's psychological well-being (psychological stressors; Lazarus & Folkman, 1984). *Distress* is a negative psychological response to such threats and can include a variety of affective and cognitive states, such as anxiety, sadness, frustration, the sense of being overwhelmed, or helplessness. Researchers have proposed a number of stressor taxonomies, most of which differentiate threats to basic physiological needs or physical integrity, social connectedness, sense of self, and resources. A number of properties of stressful circumstances can influence the severity of the psychological and physiological response. These properties include the stressor's controllability (whether responses can affect outcomes of the stressor), ambiguity, level of demand placed on the individual, novelty, and duration.

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PHYSIOLOGICAL EFFECTS OF EXPOSURE TO STRESSFUL LIFE EXPERIENCE

Extensive research in humans and other animals has demonstrated powerful effects of exposure to stressors on a variety of physiological systems. These specific changes are believed to have evolved to support the behaviors that allow the organism to deal with the threat (e.g., to fight or flee). In order for the organism to respond efficiently, physiological systems that are needed to deal with threats are mobilized and physiological systems that are not needed are suppressed. For example, when responding to a threat, the body increases available concentrations of glucose (an energy source) to ready the organism for physical activity; at the same time, the body inhibits processes that promote growth and reproduction. Although the body is adapted to respond with little ill effect to this acute mobilization, chronic or repeated activation of systems that deal with threat can have adverse long-term physiological and health effects (McEwen, 1998; Sapolsky, 1992). A wide array of physiological systems have been shown to change in response to stressors; in this section, I summarize the effects on the three most carefully studied systems (Fig. 1).

Impact on the Autonomic Nervous System

Since Walter Cannon's work on the fight-or-flight response in the 1930s, researchers have been interested in the effects of stressful experience on the

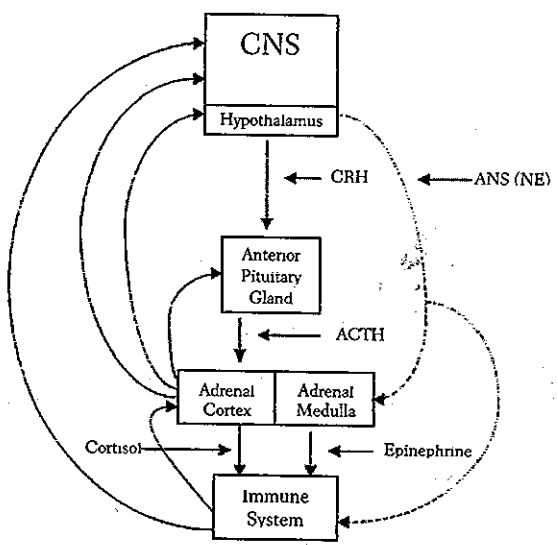

Fig. 1. Schematic representation of interrelationships among the central nervous system (CNS), the hypothalamic-pituitary-adrenal axis, the autonomic nervous system (ANS), and the immune system. Dashed lines indicate ANS neural pathways, and solid lines indicate hormonal pathways. ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; NE = norepinephrine.

sympathetic adrenomedullary system (the system is so named because the sympathetic nervous system and adrenal medulla are its key components; see Fig. 1). Cannon correctly proposed that exposure to emergency situations results in the release of the hormone epinephrine from the adrenal medulla (the core of the adrenal gland, located above the kidney). This effect was shown to be accomplished by the activity of the autonomic nervous system (ANS). The ANS has two components: the *parasympathetic nervous system*, which controls involuntary resting functions (activation of this system promotes digestion and slows heart rate, e.g.), and the *sympathetic nervous system*, which comes into play in threatening situations and results in increases in involuntary processes (e.g., heart rate and respiration) that are required to respond to physical threats. Fibers of the sympathetic nervous system release the neurotransmitter norepinephrine at various organ sites, including the adrenal medulla, causing the release of epinephrine (also known as adrenaline) into the bloodstream. Research has demonstrated that exposure to a variety of stressors can activate this system, as manifested by increased output of norepinephrine and epinephrine, as well as increases in autonomic indicators of sympathetic arousal (e.g., increased heart rate). This extremely rapid response system can be activated within seconds and results in the "adrenaline rush" that occurs after an encounter with an unexpected threat.

Impact on the Hypothalamic-Pituitary-Adrenal Axis

A large body of literature suggests that exposure to a variety of acute psychological stressors (e.g., giving a speech, doing difficult cognitive tasks), for relatively short durations, can cause an increase in the levels of the hormone cortisol in the blood, saliva, and urine. This increase is due to activation of the hypothalamic-pituitary-adrenal (HPA) axis (see Fig. 1). Neural pathways link perception of a stressful stimulus to an integrated response in the hypothalamus, which results in the release of corticotropin-releasing hormone. This hormone stimulates the anterior part of the pituitary gland to release adrenocorticotropic hormone, which then travels through the blood stream to the adrenal glands and causes the adrenal cortex (the outer layer of the adrenal gland) to release cortisol (in rodents this hormone is called corticosterone). The activation of this entire system occurs over minutes rather than seconds (as in the case of the ANS). The peak cortisol response occurs 20 to 40 min from the onset of acute stressors. Recovery, or the return to baseline levels, occurs 40 to 60 min following the end of the stressor on average (Dickerson & Kemeny, 2002).

Impact on the Immune System

Exposure to stressful experiences can diminish a variety of immune functions. For example, stressful life experiences, such as bereavement, job loss, and even taking exams, can reduce circulating levels of classes of immunological cells called lymphocytes; inhibit various lymphocyte functions, such as the ability to proliferate when exposed to a foreign substance; and slow integrated immune responses, such as wound healing (Ader, Felten, & Cohen, 2001). Individuals' autonomic reactivity to stressors correlates with the degree to which their immune system is affected by acute laboratory stressors. Extensive evidence that

autonomic nerve fibers innervate (enter into) immune organs and alter the function of immune cells residing there supports the link between the ANS and the immune system. In addition, some of the immunological effects of stressors are due to the potent suppressive effects of cortisol on immunological cells. Cortisol can inhibit the production of certain cytokines (chemical mediators released by immune cells to regulate the activities of other immune cells) and suppress a variety of immune functions.

Exposure to stressors can also enhance certain immune processes, for example, those closely related to inflammation. Inflammation is an orchestrated response to exposure to a pathogen that creates local and systemic changes conducive to destroying it (e.g., increases in core body temperature). However, chronic, inappropriate inflammation is at the root of a host of diseases, including certain autoimmune diseases such as rheumatoid arthritis, and may play a role in others, such as cardiovascular disease. There is a great deal of current interest in factors that promote inappropriate inflammation outside the normal context of infection. Exposure to some psychological stressors can increase circulating levels of cytokines that promote inflammation, perhaps because stressful experience can reduce the sensitivity of immune cells to the inhibitory effects of cortisol (Miller, Cohen, & Ritchey, 2002).

Not only can the brain and peripheral neural systems (systems that extend from the brain to the body—e.g., the ANS and HPA axis) affect the immune system, but the immune system can affect the brain and one's psychological state. In rodents, certain cytokines can act on the central nervous system, resulting in behavioral changes that resemble sickness (e.g., increases in body temperature, reduction in exploratory behavior) but also appear to mimic depression (e.g., alterations in learning and memory, anorexia, inability to experience pleasure, reductions in social behavior, alterations in sleep, behavioral slowing). Emerging data indicate that these cytokines can induce negative mood and alter cognition in humans as well. These effects may explain affective and cognitive changes that have been observed to be associated with inflammatory conditions. They may also explain some depressive symptoms associated with stressful conditions (Maier & Watkins, 1998).

Health Implications

Activation of these physiological systems during exposure to a stressor is adaptive in the short run under certain circumstances but can become maladaptive if the systems are repeatedly or chronically activated or if they fail to shut down when the threat no longer exists. McEwen (1998) has coined the term *allostatic load* to refer to the cumulative toll of chronic overactivation of the physiological systems that are designed to respond to environmental perturbations. For example, evidence suggests that chronic exposure to stressors or distress (as in posttraumatic stress disorder and chronic depression) can cause atrophy in a part of the brain called the hippocampus, resulting in memory loss. Chronic exposure to stressful circumstances has also been shown to increase vulnerability to upper respiratory infections in individuals exposed to a virus. Researchers have observed effects on other health outcomes as well, but complete models of stress and health that document all the mediating mechanisms from the central nervous system to the pathophysiological processes that control disease are not yet available (Kemeny, 2003).

GENERALITY VERSUS SPECIFICITY IN THE PHYSIOLOGICAL RESPONSE TO STRESSORS

The central dogma of most stress research today is that stressors have a uniform effect on the physiological processes I have just described. Hans Selye shaped the thinking of generations of researchers when he argued that the physiological response to stressful circumstances is nonspecific, meaning that all stressors, physical and psychological, are capable of eliciting the triad of physiological changes he observed in his rodent research: shrinking of the thymus (a central immune organ), enlargement of the adrenal gland (which produces corticosterone), and ulceration of the gastrointestinal tract. Very little research has directly tested this *generality model* by determining whether or not differences in stressful conditions are associated with distinctive physiological effects in humans. Modern versions of the generality model propose that if stressors lead to the experience of distress (or perceived stress), then a stereotyped set of physiological changes will be elicited in the systems I have described. These models also emphasize the important role of a variety of psychological and environmental factors that can moderate the relationships among stressor exposure, distress, and physiological activation (see Fig. 2). However, these newer versions are essentially generality models because all of the factors are considered relevant to the extent that they buffer against or exacerbate the experience of distress, without considering that different kinds of distress (e.g., different emotional responses) might have distinctive physiological correlates. According to these models, distress has a uniform relationship to physiology.

There is, however, increasing evidence for specificity in the relationship between stressors and physiology. Weiner (1992) advocated an integrated specificity model of stressor physiology, arguing that "organisms meet . . . challenges and dangers by integrated behavioral, physiological patterns of response that are appropriate to the task" (p. 33). According to this model, both behavior and physiology are parts of an integrated response to address a specific environmental condition (see Fig. 3), and specific conditions or environmental signals

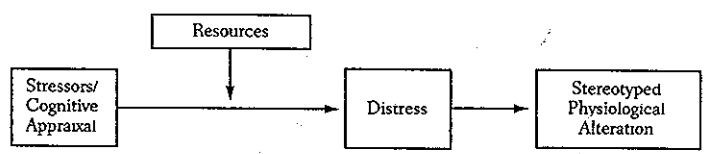

Fig. 2. The generality model of stress. This model proposes that exposure to stressors and the cognitive appraisals of those events can lead to distress. The nature of this relationship depends on the resources available to deal with the stressors (e.g., coping skills, social support, personality factors, genetics, environmental resources). Elevations in distress cause a stereotyped physiological alteration in stress-responsive systems. Bidirectional relationships between many components of the model are assumed but are not indicated here.

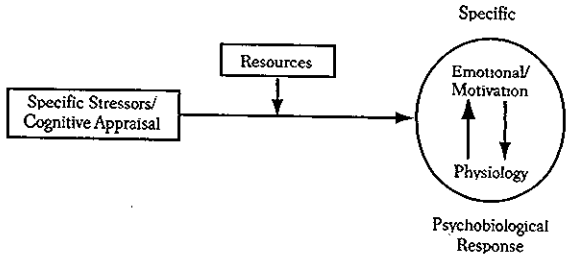

Fig. 3. The integrated specificity model of stress. This model proposes that exposure to specific stressful conditions and cognitive appraisals of those conditions shape the specific nature of an integrated psychobiological response (including emotion-motivation and physiology) to promote adaptive responses to the threat. For example, threats that are appraised as uncontrollable may lead to an integrated psychobiological response that includes disengagement from the goal that is threatened by the stressor (manifested in withdrawal, inactivity, and reduced effort), related affective states (e.g., depression), and physiological changes that support disengagement. Threats appraised as controllable may lead to an integrated response involving engagement with the threat and physiological responses supporting active coping processes. As in the generality model, resources available to deal with the stressors can moderate this relationship.

elicit a patterned array of hormonal and neural changes that are designed to ready the organism to deal with the specific nature of the threat. In animals, specific neural and peripheral changes occur in concert with behaviors such as fighting, fleeing, defending, submitting, exerting dominance, and hunting prey, among others. Distinctive behaviors (fight, flight, and defeat) have also been elicited by activating specific regions of the brain with excitatory amino acids.

COGNITIVE APPRAISALS SHAPE PHYSIOLOGICAL RESPONSES

Cognitive appraisal processes can profoundly shape the specific nature of the physiological response to stressful circumstances and play a central role in the integrated specificity model. Cognitive appraisal is the process of categorizing a situation in terms of its significance for well-being (Lazarus & Folkman, 1984). Primary appraisal relates to perceptions of goal threat, whereas secondary appraisal relates to perceptions of resources available to meet the demands of the circumstance (e.g., intellectual, social, or financial resources). Three categories of cognitive appraisals have been shown to elicit distinctive affective and physiological responses.

Threat Versus Challenge

According to Blascovich and Tomaka (1996), the experience of threat results when the demands in a given situation are perceived to outweigh the resources. When resources are perceived to approximate or exceed demands, however, the individual experiences a challenge response. These two motivational states are associated

with distinctive ANS alterations. In situations that require active responses to obtain a goal, challenge is associated with increases in sympathetic arousal (increased cardiac performance) coupled with reduced or unchanged peripheral resistance (resistance to blood flow). These changes parallel those observed with metabolically demanding aerobic exercise. Threat, in contrast, although also associated with sympathetic arousal involving increased cardiac performance, is associated with *increased* peripheral resistance, leading to increased blood pressure. Thus, different cognitive appraisals can result in distinctive patterns of ANS reactivity with potentially distinguishable implications for health. The issue here is not degree of activation of the sympathetic nervous system, but rather distinctive qualities of activation depending on the specific nature of the cognitive appraisal process.

Perceived Control

Animal and human research demonstrates that uncontrollable circumstances, or those perceived as uncontrollable, are more likely to activate key stressor-relevant systems than are circumstances that the organism perceives to be controllable. For example, when rodents with and without control over exposure to identical stressors are compared, those with control show a reduced cortisol response. A meta-analysis (a statistical analysis that summarizes findings across studies) has demonstrated that humans who are exposed to stressors in an acute laboratory context are significantly more likely to experience HPA activation if the stressors are uncontrollable than if they are controllable (Dickerson & Kemeny, 2002). Threats that are appraised as controllable but in fact are uncontrollable have been shown to elicit less severe physiological alterations (e.g., in the immune system) than those appraised as uncontrollable.

Social Cognition

The social world has a powerful effect on stress-relevant physiological systems (Cacioppo, 1994). For example, social isolation has a very significant effect on health, which is likely mediated by the physiological systems described here. Other social processes can regulate physiological systems as well. For example, place in a dominance hierarchy has a significant effect on physiological systems. Subordinate animals, who have low social status, demonstrate a more activated HPA axis, higher levels of cytokines that promote inflammation, and other physiological changes compared with their dominant counterparts. A meta-analytic review has demonstrated that demanding performance tasks elicit HPA activation when one's social status or social self-esteem is threatened by performance failures, but these effects are greatly diminished when this social-status threat is not present (Dickerson & Kemeny, 2002). Cognitive appraisals of social status and social self-esteem appear to play an important role in these effects (Dickerson, Gruenewald, & Kemeny, in press).

CONCLUSIONS

The research findings on cognitive appraisal and physiological systems lead to two important conclusions. First, depending on the nature of the eliciting conditions, different patterns of physiological response can occur. Second, when

cognitive appraisals of conditions are manipulated, distinctive physiological effects can be observed within the same context. Therefore, the way the individual thinks about the situation may override the impact of the specific nature of the conditions themselves.

In the integrated specificity model of stressful experience, stressful conditions and appraisals of them elicit integrated psychobiological responses (including emotion and physiology) that are tied to the nature of the threat experienced. A number of researchers have found that different neural and autonomic pathways are activated during different emotional experiences. Thus, specific emotions, in all likelihood, play a central role in the nature of the physiological response to stressful conditions. A more intensive evaluation of the role of distinct emotions would be an important contribution to future stress research. It is most likely that distinctions will be observed when researchers evaluate patterns of physiological change across systems, rather than relying on single response systems (e.g., cortisol level), and when emotional behavior is assessed in conjunction with self-report data.

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Acknowledgments—This article is dedicated to the memory of Herbert Weiner, a pioneer in the field of stress research, who profoundly shaped the thinking of the generations of stress researchers he trained.

Note

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