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Stress, Energy, and Immunity:

An Ecological View

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Abstract

A common perspective on stress-related changes in the human immune system is that such changes are potentially harmful, especially those occurring during chronic stress. In contrast, an ecological perspective views the immune system as an energetically costly system that may or may not have priority over other uses of that energy. From this perspective, the immune system may have energy made available for it via reduction of other activities, may change in energetically conservative ways when the protection it confers needs to be balanced with the energetic demands of other activities such as fight or flight, or may be suppressed when other activities are more important than immunity for total well-being. This last type of change can explain why aspects of psychosocial health such as optimism relate to worse immunity under some circumstances and suggests that both benefits and costs of immunosuppression during stress should be considered in research on human stress and immunity.

Keywords

ecological immunology; stress; sickness behavior

The immune system comprises cells and organs whose functions can be overgeneralized as follows: (a) to recognize non-self entities such as viruses, bacteria, and parasites in the body and (b) to destroy them. These two simple aims are accomplished via a complex regulatory network of organs, cells, cell receptors, and proteins. It was once believed that this network was shielded from outside influences (e.g., the environment or other organs) to maintain its balance. However, accumulated evidence demonstrates that the immune system is highly integrated with the nervous system, allowing it to respond to changes in the psychosocial environment. In humans, stressful events reliably associate with changes in the immune system (Segerstrom & Miller, 2004). One perspective on this evidence views stress-related decreases in immune functions as maladaptive. From this perspective, changes in the immune system resulting from stress could be harmful and a person showing such changes in the immune system is not functioning optimally. The state of the immune system reflects the health, possibly including the mental health, of the person.

This is a useful perspective, but it fails to explain why the most psychologically healthy individuals sometimes have the least robust immune systems (Segerstrom, 2005). To explain these effects, it becomes necessary to view the immune system in a broader context. *Ecological immunology* considers immunity to be just one of an organism's many potential priorities (Barnard & Behnke, 2001). In fact, unlike organs such as the heart and brain, the immune system demands high priority only when an infection is present, and too much immune activity in the absence of infection can be harmful to health. For example, excessive

inflammation has been linked to higher risk for Alzheimer's disease, heart disease, and cancer (Ershler & Keller, 2000; Ross, 1999). In addition, unnecessarily allocating energy to the immune system means that there is less energy available for other physiological or behavioral projects. From this perspective, health is not necessarily reflected in the functioning of the immune system, but in whether that functioning is adaptively prioritized.

THE COST OF IMMUNITY AND SICKNESS BEHAVIOR

Reviews of the immune system and its functions require volumes; however, it is useful to consider some of the ways immune responses may be energetically expensive. One of the best known is fever, which is caused by proteins called cytokines that are produced by activated immune cells. Fever comes at a metabolic cost: A 175-pound man would require more than 250 calories daily to maintain a fever of approximately 2° Fahrenheit. To put that expenditure in context, the same man requires 373 calories daily for his brain and 168 calories daily for his heart (Elia, 1992). Other immune activities that require energy include producing proteins and generating new immune cells in order to fight infection (Buttgereit, Burmester, & Brand, 2000).

In the face of infection, calories must be made available for the increased energetic demands of the immune system. Sick animals and humans provide such calories with a dramatic decrease in activity caused by increased fatigue and decreased interest in pleasurable pursuits such as food, socializing, and sex (Larson & Dunn, 2001). The responses of sleep and withdrawal that dominate sickness behavior conserve energy that is then available for use by the immune system. Sickness behavior is initiated by the host and not by the infectious agent; these changes can also be induced by experimental injection with a noninfectious substance that activates the immune system. Furthermore, this response has been conserved during evolution. Even caterpillars and crickets show decreased interest in food and courtship during infection (Adamo, 2006).

THE ECOLOGY OF STRESS: IMMUNOLOGICAL RESPONSES

Other circumstances demand that energy be spent elsewhere. Arguably the most famous physiological response to stress is "fight or flight," in which cardiovascular and respiratory changes such as increased heart rate provide physiological support for physical effort. Physical effort requires energy; therefore, one might predict that the immune system would be a low priority during fight-or-flight-type stressors. However, fighting and fleeing increase the risk of being wounded by bites or scrapes, and wounds provide entrances for infectious agents. Acute stressors induce an immunological profile in which low-energy-consuming immune components are enhanced and high-energy-consuming ones are suppressed (Segerstrom & Miller, 2004). Specifically, cells and antibodies that are already prepared to act are mobilized into the saliva and the blood; such mobilization comes at a relatively low energetic cost. At the same time, cell production in the blood, which comes at a relatively high energetic cost, is inhibited. The consequence appears to be a maximization of immunity while minimizing energy expenditure.

In contrast with fight or flight, stressors lasting from days to years are associated with suppression of a number of different immune functions, including protein production, cell production, and cell function (Segerstrom & Miller, 2004). As noted above, such changes are often interpreted as a strictly maladaptive cost of stress. However, from an ecological perspective, there is a possibility that such changes result from an adaptive weighing of the costs and benefits of immunity versus other potential uses of energy.

Chronic stress typically involves threatened resources. One model states that stress occurs when demands tax or exceed available resources (Lazarus & Folkman, 1984). Another

conceptualizes stress as any resource loss, whether or not it is excessive (Hobfoll, 1988). It is important for well-being to minimize losses in resources such as social integration that are strongly positively associated with human health (House, Landis, & Umberson, 1988). Therefore, when resources are threatened, it could be adaptive for organisms to direct energy away from the immune system and toward protecting or restoring their resources—that is, resolving the stress. Where might such energy go? One possibility is that resource protection involves physical activity (e.g., fighting), so the muscles would need additional glucose. However, in modern life, humans are more likely to use mental and motivational mechanisms such as planning and persistence to cope with stressors; such strategies also require glucose, but by the brain rather than the muscles (Fairclough & Houston, 2004).

This perspective does not contradict more conventional predictions regarding stress and immunity, although it posits a different underlying motivational state. However, ecological immunology expands beyond conventional views insofar as it predicts decreases in immunity in the absence of resource loss. Specifically, pursuing new resource opportunities might result in decreases in immunity if the costs of suppressing immunity were outweighed by the benefits of the resources. In the laboratory, mice who were preparing to acquire a physical or social resource (e.g., social dominance, a mating opportunity, or a nest box) had more severe parasitic infections (Barnard & Behnke, 2001). These data suggest that stress, as defined by resource loss, is only one situation in which the immune system could be suppressed in order to make energy available: Opportunity for resource acquisition is another.

Figure 1 gives a theoretical illustration of how the optimum of immune function could change as a function of the costs and benefits of the energy used to maintain it. The benefits of higher immune function include improved protection against infection. However, there are also costs that include the toxicity of chronic immune activation (line a). The corresponding optimum (a) maximizes benefit while minimizing cost. The optimum will change if either benefits or costs change. In the case of chronic stress, the energy used by the immune system represents a lost opportunity to spend that energy remediating resource loss, so opportunity costs increase (line b), and the optimum (b) decreases.

OPTIMISM AND IMMUNOSUPPRESSION

One strength of the ecological model is that it can explain relationships among psychological strengths, resources, and immunity that are not accommodated by models that equate suppression of the immune system with stress. An example of such a relationship is that between dispositional optimism—the generalized expectation of more good things in the future than bad—and cellular immunity. When circumstances are stressful but not excessively demanding, dispositional optimism is generally associated with more robust immunity (Segerstrom, 2005). This relationship is expectable, because dispositional optimists typically report less subjective experience of stress than their pessimistic counterparts do.

However, under more demanding circumstances (e.g., when stressors are less controllable or more enduring), dispositional optimism is generally associated with less robust immunity, a finding that cannot be explained by models that equate immunosuppression with stress. Figure 2 shows a representative result from law-school students who were experiencing high demand for time and energy and another group of law students who were experiencing lower demand. Under the more difficult circumstance, optimism (as measured by the Life Orientation Test–Revised) was negatively associated with delayed-type hypersensitivity responses, a measure of immune responsiveness in the skin. This relationship was not due to the effects of stress as reflected in, for example, negative mood (Segerstrom, 2006). The

other possibility is that energetic demands of coping with difficult stressors are greater among optimists, who are more likely to use active than passive coping strategies, both cognitive and behavioral (Solberg Nes & Segerstrom, 2006).

These counterintuitive relationships occur under only the most stressful conditions, suggesting that ecological effects (i.e., lowering the immune system's priority) do not occur routinely. The mere presence of stressors is insufficient to elicit these effects. For example, when stressors were controllable, brief, or simple to manage, optimists had higher immune cell numbers and function than pessimists did. Only the most difficult stressors reversed this relationship (Segerstrom, 2005). It is sensible that humans and other organisms evolved to have effective energetic resources for their everyday activities and only need to engage in energetic decision making under unusual circumstances.

ECOLOGICAL IMMUNOSUPPRESSION: WHAT IS THE RISK?

A related issue pertains to the cost of ecological immunosuppression. Although global terms such as "immunity" or "immunosuppression" are commonly used as shorthand for effects on specific components of the immune system, most studies demonstrate changes in one component of the immune system that do not necessarily imply changes in disease resistance. Furthermore, normal ranges for immune parameters are quite large. Changes in the immune system within this range are not pathological under most circumstances. However, such changes could be more critical when the immune system is already compromised. With age or immune pathologies such as HIV, the immune system becomes less resilient and potentially less able to recover from episodes of immunosuppression. The potential for ecologically driven changes to be pathological is therefore greatest among those who are already immunologically compromised. For example, HIV selectively infects and depletes helper T cells, so reconstituting "temporary" losses of helper T cell number or function might not be possible for an HIV-infected person.

Another potential cost involves a physiological mechanism that may induce ecological suppression of the immune system. The hormone cortisol simultaneously makes more glucose available from energy stores and suppresses certain physiological activities such as immune activity and reproduction. Elevated cortisol is associated with stress and distress, but like immune function, it is also associated with mental exertion and persistence and with higher dispositional optimism (Solberg Nes, Segerstrom, & Sephton, 2005). Although cortisol generally suppresses immunity, cortisol receptors on immune cells can become desensitized after prolonged periods of cortisol elevation. Immunity, particularly inflammation, can thereby escape the control that cortisol normally provides (Miller, Cohen, & Ritchey, 2002). As noted above, elevated markers of inflammation are risk factors for several serious, chronic diseases. One possibility is that ancestral environments were characterized more by risk from infection than by risk from chronic disease and that inflammation adaptively compensated for the loss of more energetically costly forms of immunity. However, chronic disease is a more serious health risk than infection in the modern environment. Ecological immunosuppression leading to rebound inflammation and increased risk for chronic disease could therefore pose a health threat to modern humans.

THE FUTURE OF STRESS AND IMMUNITY

The focus on stress in human ecology and its effects on the immune system has been useful and productive (Segerstrom & Miller, 2004). However, evidence that does not fit common conceptualizations of stress and its buffers (e.g., the relationship between dispositional optimism and cellular immunity) suggests that this focus should be broadened to encompass a cost-benefit analysis of environmental opportunities and demands and energetic resources. Although most stress models theoretically include both costs and benefits, the focus has

typically been on costs. The strategies and motivations that result in downward regulation of immunity may optimize the alleviation of stressful circumstances, the acquisition of important resources, or both.

The theoretical and empirical future of ecological perspectives on stress and human immunity might incorporate three important advances: First, research should examine both short- and long-term costs and benefits. Short-term immunosuppression has certain possible costs, but what behavioral and physiological strategies ultimately result in the best health? Long-term follow-ups should be employed to see whether certain immune changes that appear detrimental in the short term correlate with better long-term health. This question is particularly important with regard to people whose immune systems are already compromised (e.g., the elderly). Is it in the best long-term interests of those who are at immunological risk to conserve resources or energy?

Second, the resources and situations that are most likely to elicit ecologically motivated immunosuppression should be better characterized. For example, epidemiological data suggest that social relationships are among the most important human resources. Situations that threaten social resources or, alternatively, pose opportunities for social-resource gain seem likely candidates to elicit suppression of immunity. Although social networks can act as buffers against stress, they can also demand significant energy to maintain, and there is some empirical support for ecological effects with regard to social involvement. For example, clinical colds were most common among students with both high levels of stressful life events and large social networks (Hamrick, Cohen, & Rodriguez, 2002).

Third, an ecological model invites the examination of how stress and resources affect other organ systems. Some organ systems have high energetic priority at all times (i.e., the brain and heart), but others can be spared when necessary. Ecological immunology points to the immune system as one of those that can be spared, but others may be affected as much or more by the same mechanisms. The liver and kidneys, for example, are more energetically greedy than the immune system on an ongoing basis. They nonetheless lose their energetic priority during fight-or-flight stressors, as reflected in major decreases in blood supply. It would be an important piece of evidence for ecological models of stress to demonstrate that organs other than the immune system lose energetic priority in circumstances when energy is at a premium.

The immune system is undeniably important in promoting health and well-being by preventing infectious disease. However, optimal immune function is not required for survival under most circumstances, and organisms—including humans—may adaptively take energy away from the immune system in order to support other pursuits. Such ecological effects can explain perplexing anomalies (e.g., when putative stress buffers such as optimism associate with greater suppression of immunity) and point toward important new directions in human psychoneuroimmunology.

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Recommended Reading

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Fig. 1.

Theoretical costs and benefits associated with increasing immune function, as suggested by Råberg, Grahn, Hasselquist, & Svensson (1998). Benefits of immune function include ability to fight infection; costs include the potential for over-response (e.g., excessive inflammation or autoimmune disease) and opportunity costs of the energy used (e.g., other activities or resources not pursued in order to make energy available for immune activity). When costs, including opportunity costs of the energy used, are low (a), the optimum for immune function is higher than it is when costs are higher (b); in that case, the optimum decreases. Adapted from “On the Adaptive Significance of Stress-Induced Immunosuppression,” by L. Råberg, M. Grahn, D. Hasselquist, and E. Svensson, 1998, *Proceedings of the Royal Society of London – B*, 265, p. 1638. Copyright 1998, The Royal Society of London. Adapted with permission.

Fig. 2.

Relationship between dispositional optimism and cellular immune responses (predicted induration) as a function of how demanding a stressful circumstance is. The figure is a representative example from first-year law students (Segerstrom, 2006). Induration is the size (in millimeters, mm) of the response to an immune challenge in the skin. Adapted from “How Does Optimism Suppress Immunity? Evaluation of Three Affective Pathways,” by S.C. Segerstrom, 2006, *Health Psychology*, 25, p. 655. Copyright 2006, American Psychological Association. Adapted with permission.