Stress, Adaptation, and Disease

Allostasis and Allostatic Load

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ABSTRACT: Adaptation in the face of potentially stressful challenges involves activation of neural, neuroendocrine and neuroendocrine-immune mechanisms. This has been called "allostasis" or "stability through change" by Sterling and Eyer (Fisher S., Reason J. (eds): *Handbook of Life Stress, Cognition and Health.* J. Wiley Ltd. 1988, p. 631), and allostasis is an essential component of maintaining homeostasis. When these adaptive systems are turned on and turned off again efficiently and not too frequently, the body is able to cope effectively with challenges that it might not otherwise survive. However, there are a number of circumstances in which allostatic systems may either be overstimulated or not perform normally, and this condition has been termed "allostatic load" or the price of adaptation (McEwen and Stellar, *Arch. Int. Med.* 1993; 153: 2093.). Allostatic load can lead to disease over long periods. Types of allostatic load include (1) frequent activation of allostatic systems; (2) failure to shut off allostatic activity after stress; (3) inadequate response of allostatic systems leading to elevated activity of other, normally counter-regulated allostatic systems after stress. Examples will be given for each type of allostatic load from research pertaining to autonomic, CNS, neuroendocrine, and immune system activity. The relationship of allostatic load to genetic and developmental predispositions to disease is also considered.

Stress is a common experience in our daily lives that is blamed for causing or exacerbating many ills—heart disease, cancer, asthma, GI disturbances, the common cold—and yet we have very little idea of how stressful experiences may lead to disease. There are at least three reasons for this. First, our concept of stress is very subjective and does not take into account the enormous individual differences that exist in coping with the environment. Second, there are many aspects of daily life that may not qualify as stress but nevertheless may have adverse effects on the body; however, it is difficult to measure the physiological price of these daily hassles except as they cumulate and result in a pathophysiological change or a disease. Third, and related to the second point, we do not fully appreciate the operation of the systems of the body that promote adaptation and promote homeostasis through their ability to respond to challenges, because these systems can also cause damage under extreme circumstances. This notion was at the basis of the formulation of the "glucocorticoid-cascade hypothesis" of aging.[1,2]

These systems, such as the autonomic nervous system and hypothalamo-pituitary-adrenal axis, promote adaptation, a process called "allostasis" by Sterling and Eyer,[3] but these allostatic systems can also cause problems for the body if they

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are overactive or underactive. Thus, adaptation, or allostasis, often has a price; and we have called the price of adapation that promotes pathophysiology "allostatic load."[4] Allostatic load results when the allostatic systems are either overworked or fail to shut off after the stressful event is over or when these systems fail to respond adequately to the initial challenge, leading other systems to overreact.

This article will briefly summarize these concepts. After a discussion of allostasis and allostatic load, we then discuss how these concepts apply to the operation of the immune system.

INDIVIDUAL DIFFERENCES IN RESPONSE TO CHALLENGE

There are enormous individual differences in how people respond to potentially stressful situations, and these depend on two principal factors. (See FIG. 1.) The first is how the individual perceives and interprets the situation—if as a threat, then behaviors and physiological responses ensue that can have further consequences; if the situation is not perceived as a threat, then the responses either don't occur or are quite different and more benign. For example, it has been documented that most people respond to a public-speaking challenge with increased salivary cortisol levels but habituate rapidly with repetition of the challenge; nevertheless, a minority of individuals fail to habituate their cortisol response, and these persons have the characteristic of low self-esteem.[5]

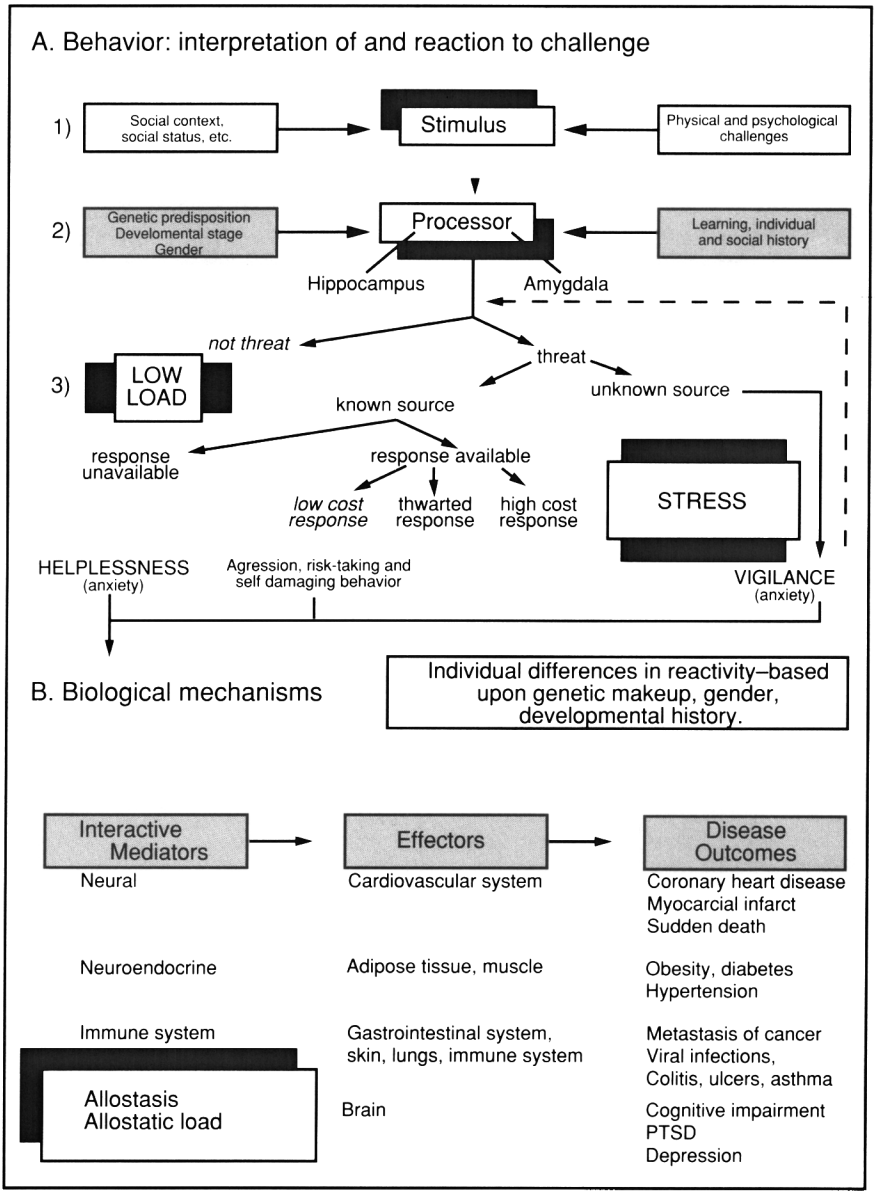
The second aspect of individual differences concerns the condition of the body itself. For example, people who are in good physical condition can handle strenuous exercise far better than those not in shape. Moreover, metabolic imbalances that lead to obesity and diabetes can increase the vulnerability of an individual to stress, and these may have a genetic component.[6] For Type I diabetes, the BB rat strain responds to stress by increasing the number of individuals that express the disease,[7] and evidence for human Type I diabetes shows that life stressors increase the incidence and severity of the disease in children.[8] Relevant to Type II diabetes, stress increases fat deposition in experimental animals,[9] and data for humans indicates that stressful life events accelerate the course of the disease.[10,11]

THE BRAIN AS A TARGET OF STRESS

Repeated stress has consequences for brain function, especially the hippocampus, which is endowed with high levels of receptors for adrenal steroids. The hippocampus participates in episodic and declarative memory and is especially important for the memory of "context," that is, the time and place where events

FIGURE 1. Diagram depicts behavioral mechanisms that interpret events and experiences as threatening and therefore likely to be stressful in a physiological sense and the physiological responses and related diseases that are likely to be affected by those events. Also shown are the behavioral responses in terms of whether there is a response available and whether the response involves a high or low cost, in terms of further potentially stressful or harmful interactions. For example, behaviors that remove the individual from danger are low cost, whereas behaviors that involve further confrontation are high-cost responses. Drinking, smoking, and engaging in risky physical activity (e.g., driving recklessly) are also high-cost responses.

occur that have a strong emotional bias.[12–14] Consequently, impairment of hippocampal function decreases the reliability and accuracy of such memories, and this may contribute to the degree to which events may be perceived as stressful when their circumstances might otherwise have been perceived as nonthreatening if context memory functions had been normal. The hippocampus is also a regulator of the stress response and exerts a largely inhibitory effect to promote shut-off



of the HPA stress response.[15] Recent evidence suggests that the hippocampal influence on the hypothalamic CRF neurons is via the bed nucleus of the stria terminalis and involves the regulation of an inhibitory input to these neurons.[16]

The mechanism for stress-induced hippocampal dysfunction and memory impairment is twofold. First, acute stress elevates adrenal steroids and suppresses neuronal mechanisms that subserve short-term memory involving the hippocampus and temporal lobe.[17,18] These effects are reversible and relatively short-lived. Second, repeated stress causes an atrophy of dendrites of pyramidal neurons in the CA3 region of the hippocampus, and it does so through a mechanism involving both glucocorticoids and excitatory amino acid neurotransmitters released during and in the aftermath of stress.[19] Although this atrophy is reversible as long as stress is short-lived, prolonged stress lasting many months or years appears to be capable of killing hippocampal neurons.[2,20] Stress-related disorders such as recurrent depressive illness, post-traumatic stress disorder, and Cushing's syndrome are associated with atrophy of the human hippocampus measured by MRI.[21,22] It is not yet clear to what extent this atrophy represents a reversible process or permanent neuronal loss.

Long-term stress also accelerates a number of biological markers of aging in rats, including increasing the excitability of CA1 pyramidal neurons via a calcium-dependent mechanism and causing loss of hippocampal pyramidal neurons.[23] An important factor may be the enhancement by glucocorticoids of calcium currents in hippocampus,[24] in view of the key role of calcium ions in destructive as well as plastic processes in hippocampal neurons. Another aspect of the mechanism of age-related neuronal damage is the persistence of excitatory amino acid release in hippocampus after stress in aged rats,[25] a condition that is likely to potentiate the atrophy and possibly even lead to neuronal loss in the aged brain.

Another aspect of stressful experiences is the developmental influence of early stress and of neonatal handling on the life-course of aging and age-related cognitive impairment. Such early experiences can either increase or decrease the rate of brain aging through a mechanism in which the activity of the HPA axis appears to be involved.[26,27] The early experiences are believed to set the level of responsiveness of the HPA axis and autonomic nervous system in such a way that these systems either over react in animals subject to early unpredictable stress or underreact in animals exposed to the neonatal handling procedure.[27]

HOMEOSTASIS, ALLOSTASIS, AND ALLOSTATIC LOAD

Having noted the effects of stress on the brain, and particularly on the hippocampus, we now return to the broader topic of stress and how individuals interpret and respond to stress. To do this, we discuss two concepts: "allostasis"[3] and "allostatic load,"[4] which pertain to adaptation and the cost of adaptation for the body and brain. The sensitivity and vulnerability of the hippocampus discussed above, as manifested in the interactions between excitatory amino acids, serotonin, and glucocorticoids, is an especially good example of the notion of allostasis and allostatic load, in that the release of these neuromodulators is an adaptive response (allostasis) to a potentially stressful event, whereas the long-term consequences of this allostasis is an atrophy of neuronal processes that compromise hippocampal function (allostatic load). Moreover, the role of the hippocampus in interpreting and responding to potential stressors plays an important role in determining the level of "allostatic load" that an individual will

experience, because selective attention to cues and use of contextual information based on prior experiences may improve the discriminative capability and allow the individual to respond to a potential stressor in a way that minimizes the allostatic load.

What is "allostasis"? The body has systems that respond to the body state (like waking, sleeping, lying, standing, exercising) and to the external environment and that promote adaptation to activities such as locomotion and to aversive stimuli—like noise and crowding, hostility, fatigue, isolation, hunger, excessive heat or cold—and threats to safety. These systems include the HPA axis; the autonomic nervous system; the metabolic systems—thyroid axis, insulin, glucagon, and the gut; and the immune system. They are closely coupled to the psychological makeup of the individual, in that those people who are fearful and reactive will have more reactive physiological responses, whereas those individuals who have proactive planning skills and psychological buffers will have less reactive responses and more stability in their physiology.

Adversity, including conflict and social instability, accelerates pathophysiological processes and results in increased incidence of morbidity and mortality. The cardiovascular system is one of the most susceptible. For example, blood pressure increases are a sensitive index of job stress in factory workers and other repetitive jobs with time pressures[28] and of job instability in British civil service departments undergoing privitization (Marmot, personal communication), and cardiovascular disease is a primary reason for the increased death rate in Eastern Europe in the social collapse following the fall of communism.[29] It should be noted that blood pressure surges are linked to accelerated atherosclerosis[30] as well as increased risk for myocardial infarction.[31] Besides the cardiovascular system, there are indications that metabolic disorders and abdominal obesity are increased at the lower end of the socioeconomic status gradient in Swedish males.[32] Immune system function is also a likely target,[33] with increased vulnerability to infections and possibly even to cancer, but there is far less evidence on this point.

We have noted throughout this chapter that individuals respond in different ways to adversity and threats (real or implied) to their safety and homeostasis. Physiological responses of the autonomic nervous system, HPA axis, cardiovascular, metabolic, and immune systems lead to protection and adaptation of the organism to these challenges. This process, referred to as allostasis, is an essential component of maintaining homeostasis. However, adaptation to adversity has a price, and we have come to define the cost of adaptation as *allostatic load*.[4] Much of our ability to make a breakthrough in understanding the linkage between behavior, brain function, and health depends on our making progress in defining and operationalizing the concept of allostatic load. *Allostatic load is the wear and tear on the body and brain resulting from chronic overactivity or inactivity of physiological systems that are normally involved in adaptation to environmental challenge.* Although it is true that physiological parameters like blood oxygen and pH are maintained within a narrow range (*homeostasis*), the cardiovascular system, metabolic machinery, immune system, and central nervous system all show a large range of activity as a function of the time of day and in response to external and internal demands (*allostasis*). These systems are involved in coping and adaptation, and, as a general rule, they are most useful when they can be rapidly mobilized and then turned down in their activity again when not needed. It is when they are not turned off or turned down that these systems become dangerous for health. Moreover, the inability to turn on these systems when needed also produces a load on the body, because the normal protection afforded by these systems is lacking. (See TABLE 1.)

TABLE 1. Interacting Adaptive Systems of the Body[a]

System	Acute Response to Challenge	Problems Associated with Chronic Activity or Inactivity[b]
Cardiovascular	Maintaining erect posture (avoiding "black-out") Physical exertion	Hypertension, potential for stroke, MI
Metabolic	Activating and maintaining energy reserves, including energy supply to the brain	Obesity, diabetes, atherosclerosis
Immune	Response to pathogens	Inflammatory,[b] autoimmune disorders[b]
	Surveillance for tumors	Immunosuppression
Brain, CNS	Learning, memory Neuroendocrine and autonomic regulation	Neuronal atrophy, death of nerve cells

[a]Mediators involved in modulating these adapative systems consist of hormones (principally, but not confined to, adrenalin and noradrenalin, ACTH and glucocorticoids, insulin and glucagon) and cytokines (produced not only by immune cells but also by the liver and brain). Measures of allostatic load that have been utilized in a recent study[41] include systolic and diastolic blood pressure, waist–hip ratio, cholesterol/HDL ratio, glycosylated hemoglobin, overnight urinary cortisol and catecholamines, HDL cholesterol, and DHEA-sulfate.

[b]Elevated inflammatory cytokines or autoimmune responses reflect the inadequacy of other adaptive systems like adrenal steroids, which normally inhibit and contain these responses.

An important aspect of allostasis and allostatic load is the notion of anticipation.[34] Although originally introduced in relation to explaining the reflex that prevents us from blacking out when we get out of bed in the morning,[3] anticipation also implies psychological states such as worry and anxiety as well as cognitive preparation for a coming event. Because anticipation can drive the output of mediators (this is particularly true of hormones like ACTH, cortisol, and adrenalin), it is likely that states of prolonged anxiety and anticipation can result in allostatic load.[34] However, this is one of many notions that need experimental testing.

Another important aspect of individual responses in relation to allostasis and allostatic load are the health-damaging and health-promoting behaviors such as smoking, drinking, choice of diet, and exercise (see FIG. 1). These may be regarded as part of the overall notion of allostasis—that is, how individuals attempt to cope with a challenge—and they also contribute in some ways that are known to allostatic load (e.g., a rich diet accelerates atherosclerosis and progression to Type II diabetes; smoking exacerbates blood pressure and atherogenesis; exercise has an ameliorative effect).

There are three types of physiological responses that make up allostatic load:

Type 1, *Frequent stress*: The magnitude and frequency of responses—example: blood pressure surges not only trigger myocardial infarction (MI) in susceptible individuals but their repetition also accelerates atherosclerosis and primes the risk for MI. Here it is the frequency and intensity of the "hits" or events that determine how much allostatic load of type 1 is accumulated, although type 1 allostatic load may

lead into type 2 or possibly even to type 3, as the body responds to repeated events by either failing to shut off neural and endocrine responses or failing to respond adequately. Post-traumatic stress disorder is an example of how an acute traumatic event leads to an HPA axis that may not respond adequately to acute challenge.[35]

Type 2, *Failed shut-down:* Chronic activity and failure to shut off—examples: persisently elevated blood pressure and glucocorticoids accelerate obesity and Type II diabetes; persistent glucocorticoid elevation and/or excitatory activity in the brain causes dendritic atrophy and neuronal death in the hippocampus; blood pressure elevations in repetitive, time-pressured work.[36]

Type 3, *Inadequate response:* Failure to respond to challenge—example: autoimmunity and inflammation is associated with inadequate endogenous glucocorticoid responses, as in the Lewis rat[37] and possibly also in chronic fatigue syndrome and fibromyalgia.[38–40] In this situation, other systems, such as inflammatory cytokines, show elevated activity and in this respect show an allostatic load because of the inadequate HPA activity, which normally contains their activity.

Individuals showing these patterns are likely to be distributed differently across gradients of socioeconomic status (SES) but not confined exclusively to one part of the gradient. Thus, it is important to distinguish between characteristics of groups and the vulnerability of individuals. It is necessary to study the biology–behavior interface to understand the forms of allostatic load and their relationship to diseases in individuals, which has been the subject of this chapter, while at the same time developing tools for recognizing how these traits are distributed and what aspects of the various communities in which they live may contribute to their occurrence.

One of the major challenges is determining allostatic load. An initial attempt in this direction[41] has utilized data from the MacArthur Successful Aging study to follow 10 measures of increased activity of allostatic systems between 1988 and 1991. The measures are listed in the legend to TABLE 1. Individuals were classified as to whether they were in the most extreme quartile (*highest* in systolic blood pressure; overnight urinary cortisol, catecholamines; waist/hip ratio; glycosylated hemoglobin; ratio cholesterol:HDL; *lowest* in DHEA-sulfate and HDL cholesterol). The analysis indicated that individuals who were high functioning in 1988 had lower allostatic load scores than lower functioning individuals; moreover, those higher functioning people in 1988 who had the highest allostatic load scores (most extreme quartile in at least one or more allostatic load measure) had the highest probability of showing cardiovascular disease in 1991, and they also showed the greatest decline in cognitive measures and measures of physical functioning.[41] The cognitive decline was unexpected on the basis of traditional thinking about the allostatic load measures and risk for disease, but it is quite consistent with the picture that is painted in the present review and in other chapters in this volume. Clearly, this is just the beginning of this type of analysis and much more needs to be done to test and operationalize the utility of allostatic load measures, as well as to broaden them to include immune system related-disorders and the three types of allostatic load described above.

HOW AND WHY DO ALLOSTATIC SYSTEMS MALFUNCTION AND LEAD TO ALLOSTATIC LOAD?

Allostatic load refers to an imbalance in systems that promote adaptation. As noted, this imbalance can simply be the result of too much repeated stress, but it

also can be the result of adaptive systems that are out of balance and fail to shut off or, alternatively, systems that fail to turn on adequately. The shut-off of the stress response is particularly important, because, when systems do not shut off in time, they can cause damage or promote pathology. The examples cited for the brain of failed shut-off of the HPA axis and of the output of excitatory amino acids from the hippocampus in aging rats illustrate this situation. On the contrary, when systems do not respond adequately, there are other systems whose activity is elevated as a result because they are normally counter-regulated. Inflammatory cytokines are examples of such a system that is normally counter-regulated by adrenal steroids.

How does such imbalance arise? One possibility is that repeated stress causes systems to wear out or become exhausted, leading either to the failure of shut-off or failure to respond. As proposed by Sapolsky in the glucocorticoid cascade hypothesis of stress and aging,[1,2] the wearing out of the mechanism that keeps HPA activity contained is likely to involve, at least in part, damage to the hippocampus. Evidence to support this has been obtained in studies of aging rats by finding that there are age-impaired animals with HPA hyperactivity and cognitive impairment.[26,27,42] At the other extreme, the failure to mount an adequate HPA response is a feature of the Lewis rat that results in increased vulnerability to autoimmune and inflammatory disturbances.[43,44] A stress-induced state of HPA hyporesponsiveness has been seen among rats that become subordinate in a psychosocial living situation called the "visible burrow system."[45,46] In these rats, there is a very limited HPA response to experimenter-applied stressors, and hypothalamic CRFmRNA levels are abnormally low.[46]

HOW DOES THIS AFFECT THE IMMUNE SYSTEM?

What is the meaning of allostasis and allostatic load for the immune system? In other words, how does the immune system respond to acute stress and to repeated stress? It must be emphasized that the immune system in the living body is a heterogeneous and dispersed system of cells with various functions. One of the effects of acute stress is to cause immune cells to redistribute throughout the body, and this "trafficking" is mediated in part by adrenal steroids.[47–50] Adrenal steroids cause T and B lymphocytes, NK cells, and macrophages to marginate on blood vessel walls and in the bone marrow as long as there is not a specific challenge to the immune system. When this occurs, as is the case in delayed-type hypersensitivity (DTH), immune cells traffic to the site of acute challenge, and this effect is enhanced by acute stress.[51,52] The effects of acute stress last for a number of days and are dependent on adrenal steroid secretion. Thus acute stress has the effect of calling immune cells "to their battle stations" and allostasis—the physiological response that leads to adaptation—enhances responses for which there is an immunologic memory.[51–53] If the immunologic memory is for a pathogen or a tumor cell, the result of stress is presumably beneficial. On the contrary, if the immunologic memory is for an autoimmune response or allergic response, then the stress effect is likely to exacerbate a disease process.

What happens when stress is repeated? Preliminary data indicates that, whereas acute stress enhances the DTH response, chronic stress suppresses it, resulting in a lesser effect of acute stress as well.[54] This result is consistent with the notion that allostatic load of type 1 (see above) involving frequent repeated

stress will dampen the ability of the immune system to respond acutely to stressors as well as lead to an impairment of an adaptive response. As far as type 2 allostatic load is concerned, the consequences for immune function of failed shut-off of stress-responsive hormone systems remain to be determined, although this outcome may be closely related to the consequences of type 1 allostatic load. Furthermore, repeated stress may produce such wear and tear on the system that the allostatic systems like the HPA axis and ANS become less able to shut themselves off after stress, that is, type 1 allostatic load leads to type 2 allostatic load. For type 3 allostatic load, the insufficiency of HPA reactivity in the Lewis rat[43,44] is associated with a failure of acute stress to potentiate delayed-type hypersensitivity.[51]

On the other hand, Lewis rats do respond to repeated stress and show an amelioration of EAE for which they are particularly susceptible, indicating that this aspect of the stress response is not totally lacking, only somewhat deficient.[55] This finding is a reminder of another action of repeated stress, namely, to suppress inflammatory and autoimmune processes. These actions are complex functions of both innervation and hormonal regulation of immune function and are reviewed elsewhere.[47,56] With regard to adrenal steroids, it should be noted that the immune system is somewhat protected from the actions of endogenous adrenal steroids in that organs such as the spleen and thymus do not see a large occupancy of adrenal steroid receptors because of the buffering actions of corticosteroid-binding globulin (CBG).[47,57–59] In contrast, these same organs are very accessible to synthetic steroids such as dexamethasone, which do not bind to CBG.[47,60]

CONCLUSIONS

The immune system, like the brain, is delicately balanced in terms of allostasis, so that the response to acute stress promotes allostasis or adaptation and promotes survival by protecting the body from damage. However, when the allostatic systems are overworked, the capacity to respond acutely with DTH is suppressed. Yet repeated stress can also cause a beneficial suppression of adverse inflammatory and autoimmune response,[55] indicating that the consequences of allostatic load are not all bad. On the other hand, the absence of an adequate allostatic HPA response to acute stress in the Lewis rat is associated with both a failure of stress to enhance the DTH and with an increased susceptibility to inflammatory and autoimmune processes.

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