Protection and Damage from Acute and Chronic Stress

Allostasis and Allostatic Overload and Relevance to the Pathophysiology of Psychiatric Disorders

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ABSTRACT: Stress promotes adaptation, but prolonged stress leads over time to wear-and-tear on the body (allostatic load). Neural changes mirror the pattern seen in other body systems, that is, short-term adaptation vs. long-term damage. Allostatic load leads to impaired immunity, atherosclerosis, obesity, bone demineralization, and atrophy of nerve cells in the brain. Many of these processes are seen in major depressive illness and may be expressed also in other chronic anxiety disorders. The brain controls the physiological and behavioral coping responses to daily events and stressors. The hippocampal formation expresses high levels of adrenal steroid receptors and is a malleable brain structure that is important for certain types of learning and memory. It is also vulnerable to the effects of stress and trauma. The amygdala mediates physiological and behavioral responses associated with fear. The prefrontal cortex plays an important role in working memory and executive function and is also involved in extinction of learning. All three regions are targets of stress hormones. In animal models, neurons in the hippocampus and prefrontal cortex respond to repeated stress by showing atrophy, whereas neurons in amygdala show a growth response. Yet, these are not necessarily "damaged" and may be treatable with the right medications.

KEYWORDS: stress; psychiatric disorders; depression; allostasis; allostatic overload; homeostasis

INTRODUCTION

Stress hormones and other mediators, such as neurotransmitters, cytokines, and other hormones, are essential for adaptation to challenges of daily life as well as to major life stressors. This process has been called "allostasis," that is, maintaining stability, or homeostasis, through change. When mediators of allostasis, like cortisol and adrenaline, are released in response to stressors or to lifestyle factors such as diet, sleep, and exercise, they promote adaptation and are generally beneficial. However, when these mediators are not turned off when the stress is over, or when they

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are not turned on adequately during stress, or when they are overused by many stressors,[1] there are cumulative changes that lead to a wear-and-tear, called "allostatic load or overload," on the body and brain.

Psychiatric disorders such as depression provide a good example. Stressful life events can precipitate depression, and depression is a disorder that affects the function of the whole body including the cardiovascular, metabolic, and immune system, as well as the structure and function of the brain itself.[2] In depression and other psychiatric disorders, stress hormones, such as cortisol, are involved in psychopathology, reflecting emotional arousal and psychic disorganization.[3]

Adrenocortical hormones enter the brain and produce effects upon it, ranging from steroid psychosis that can be blocked by a glucocorticoid antagonist[4] to a wide range of effects on the normal brain that include enhancement of memory.[2] The overactivity of adrenocortical hormones is associated with allostatic load. Both major depression and Cushing's disease are associated with chronic elevation and temporal dysregulation of cortisol secretion that results in gradual loss of minerals from bone and abdominal obesity as well as structural changes such as atrophy of the hippocampus and hyperactivity of the amygdala.[5,6] We examine the distinctions between allostasis and adaptation, on the one hand, and allostatic load and damage, on the other, and discuss briefly the relevance to brain-body interactions in depression and related mood and anxiety disorders.

ALLOSTASIS, ALLOSTATIC LOAD, AND OVERLOAD

The brain was once conceived as having primarily descending influences on the body, and stressors of all varieties were thought to ignite a general and diffuse arousal reaction.[7,8] Based on recent research and conceptualizations, a very different picture of integrative physiology has emerged, one in which experiences have a cumulative impact on physical and mental health and the progression of a number of specific diseases.[1] This is the result of the fact that the brain and body are in two-way communication via the autonomic nervous system and endocrine and immune systems and the fact that seemingly small changes in these systems can accumulate over time.

The terms, "allostasis" and "allostatic overload," allow for a more restricted and precise definition of the overused word "stress" and provide a view of how the essential protective and adaptive effects of physiological mediators that maintain homeostasis are also involved in the cumulative effects of daily life when they are mismanaged or overused. These terms also clarify inherent ambiguities in the concept of homeostasis, and we also note the ways in which they replace and clarify aspects of the "General Adaptation Syndrome" as formulated by the late Hans Selye.[8]

A central construct in Seyle's integrative model of stress was the notion of *homeostasis*, which refers to the stability of physiological systems that maintain life. Homeostasis is used in this article to apply strictly to a limited number of physiological variables, such as pH, body temperature, glucose levels, and oxygen tension, that are truly essential for life and are, therefore, maintained within a narrow range of values, referred to as "set points."

The concept of *allostasis* refers to the network of interacting mediators by which stability, that is, homeostasis, is achieved through change. There are primary medi-

ators of allostasis, such as, but not confined to, hormones of the hypothalamo-pituitary-adrenal (HPA) axis, catecholamines, and cytokines. These mediators interact with each other to create a network of reciprocal effects.

Allostasis, therefore, distinguishes between the systems that are essential for life (homeostasis) and those that maintain these systems in balance (allostasis). When the systems involved in allostasis are elevated in a sustained manner, this is referred to as an *allostatic state*. Originally proposed for understanding physiological aspects of drug abuse,[9] an allostatic state results in an imbalance of the primary mediators, reflecting excessive production of some and inadequate production of others.

Some examples of allostatic states are hypertension, a perturbed cortisol rhythm in major depression or after chronic sleep deprivation, chronic elevation of inflammatory cytokines and low cortisol in Chronic Fatigue Syndrome, and imbalance of cortisol, CRF, and cytokines in the Lewis rat that increase the risk for autoimmune and inflammatory disorders. Allostatic states can be sustained for limited periods if food intake and/or stored energy, such as fat, can fuel homeostatic mechanisms (e.g., bears and other hibernating animals preparing for the winter).

If imbalance continues for longer periods and becomes independent of maintaining adequate energy reserves, then symptoms of allostatic overload appear. Abdominal obesity is an example of this condition. Allostatic states, therefore, refer to altered and sustained activity levels of the primary mediators, such as glucocorticoids, that integrate energetic and associated behaviors in response to changing environments and challenges such as social interactions, weather, disease, predators, and pollution.

Allostatic states can produce wear and tear on the regulatory systems in the brain and body. Therefore, the terms *allostatic load* and *allostatic overload* refer to the cumulative result of an allostatic state (e.g., fat deposition in a bear preparing for the winter, a bird preparing to migrate, or a fish preparing to spawn is allostatic load). Allostatic load can be considered the result of the daily and seasonal routines that organisms use to obtain food and survive and to obtain extra energy needed to migrate, molt, breed, etc.[10] Within limits, they are adaptive responses to seasonal and other demands. However, if one superimposes on this additional load of unpredictable events in the environment, disease, human disturbance, and social interactions, then allostatic load can increase dramatically and become allostatic overload, serving no useful purpose and predisposing the individual to disease.

PROTECTION AND DAMAGE

Every system of the body responds to acute challenge with allostasis, putting out mediators that promote adaptation and survival. When these acute responses are overused or inefficiently managed, allostatic overload may occur.

For the *immune system,* acute stress promotes immune function by enhancing movement of immune cells to places in the body where they are needed to defend against a pathogen; yet, chronic stress suppresses immune function and uses the same hormonal mediators to suppress immune function.[11]

For the *cardiovascular system,* we see a similar paradox. Getting out of bed in the morning requires an increase in blood pressure and a reapportioning of blood flow to the head so we can stand up and not faint.[12] Blood pressure rises and falls during the day as physical and emotional demands change, providing adequate blood flow

as needed. Yet repeatedly, elevated blood pressure promotes generation of atherosclerotic plaques, particularly when combined with a supply of cholesterol and lipids and oxygen-free radicals that damage the coronary artery walls.[13] Beta-adrenergic receptor blockers are known to inhibit this cascade of events and to slow down the atherosclerosis that is accelerated in dominant male cynomologus monkeys exposed to an unstable dominance hierarchy.[14]

For *metabolism,* the paradox also is evident. Glucocorticoids, so-named because of their ability to promote conversion of protein and lipids to usable carbohydrates, serve the body well, in the short run, by replenishing energy reserves after a period of activity, like running away from a predator. Glucocorticoids also act on the brain to increase appetite for food and to increase locomotor activity and food-seeking behavior,[15] thus regulating behaviors that control energy input and expenditure. This is very useful when we do manual labor or play active sports' however, it is not beneficial when we grab a pizza and a beer while watching television or writing a paper, particularly when these activities may also be generating psychological stress, for example, watching distressing news or worrying about getting the paper done in time. Comfort foods appear to reduce anxiety by reducing activity of the HPA axis and subsequently reducing activity of the anxiogenic CRH system of the amygdala.[16] Inactivity and lack of energy expenditure create a situation where chronically elevated glucocorticoids that may result from either poor sleep or ongoing stress or as side effects of excessive intake of "comfort food" impede the action of insulin to promote glucose uptake. One of the results of this interaction is that insulin levels increase and, together, insulin and glucocorticoid elevations promote the deposition of body fat, and this combination of hormones also promotes the formation of atherosclerotic plaques in the coronary arteries.[17] Thus, whether psychological stress or sleep deprivation or a rich diet is increasing the levels of glucocorticoids, the consequences in terms of allostatic load are the same—insulin resistance and increased risk for cardiovascular disease. Thus, catecholamines and the combination of glucocorticoids and insulin can have dangerous effects on the body, besides their important short-term adaptive roles.[17]

The *nervous system* regulates the physiological and behavioral coping responses to daily events as well as major stressors, and the brain is itself a target of the mediators of those responses through circulating hormones. The amygdala and hippocampus interpret what is stressful and regulate appropriate responses. The amygdala becomes hyperactive in posttraumatic stress disorder and depressive illness, and hypertrophy of amygdala nerve cells is reported after repeated stress in an animal model. The hippocampus expresses adrenal steroid receptors. It undergoes atrophy in a number of psychiatric disorders and responds to repeated stressors with decreased dendritic branching and reduction in the number of neurons in the dentate gyrus. For the brain, the secretion of stress hormones, adrenalin and cortisol, in response to an acutely threatening event promotes and improves memory for the situation so that the individual can stay out of trouble in the future; yet, when the stress is repeated over many weeks, some neurons atrophy and memory is impaired, whereas other neurons grow and fear is enhanced.

Major depressive illness involves structural changes in areas of the brain that are involved in anxiety, memory, and decision-making, along with changes in the rest of the body as a result of long-term imbalances in hormonal and other regulatory systems.[2] Recent data from structural and functional brain imaging show that the

hippocampus, prefrontal cortex, and amygdala undergo changes in size and function with depressive episodes, and data obtained from experimental animals subjected to psychosocial and other stressors provide insights into the neurobiological mechanisms. One of the most interesting features of these structural changes in animal models is their potential reversibility with antidepressant and antiseizure medications. Another fascinating aspect is that the dentate gyrus region of the hippocampal formation continues to produce new neurons in adult life, and this neurogenesis is suppressed by acute and chronic stress and elevated by many antidepressant treatments.

LONG-TERM WEAR AND TEAR IN THE BODY FROM IMBALANCE IN REGULATORY SYSTEMS

We therefore propose that the long-term consequences of the imbalances in activity with key brain structures are imbalances in hormonal and neural regulatory systems. This, in turn, causes a wear and tear on the body that results in a number of pathophysiological consequences, because the amygdala regulates both autonomic nervous system activity and ACTH and cortisol production through outputs of its central nucleus.[18,19] It is important to note the reports that in recurrent major depression of long duration, the amygdala may undergo shrinkage.[6] It is therefore possible that initial hypertrophy, referred to earlier in this article, gives way to atrophy in this important brain structure.

Besides the brain changes in major depression, there are other changes in the body that reflect dysregulated hormonal and autonomic activity and are slow in developing.[2] In particular, the diurnal rhythm is distorted in depressive illness. Normally low evening levels of cortisol are increased in depression, and the stress hormone axis in major depression is resistant to suppression by the synthetic glucocorticoid dexamethasone. It is also noteworthy that androgen levels are elevated in women with major depression, which undoubtedly reflects adrenal hyperactivity. IGF-1 levels are also reported to be elevated in major depression, and this may reflect elevated growth hormone release as a result of the hypercortisolemia. Each of these patterns of elevation reflects allostatic states and resultant allostatic load and overload. These progressive changes may also be reversible if caught in time. Such cumulative, long-term effects include bone mineral loss and abdominal fat deposition. Moreover, the combination of long-term wear and tear, together with dysregulation of the autonomic nervous system in major depression, is associated with increased blood platelet reactivity and increased risk for cardiovascular disease.[2] Moreover, certain antidepressants may contribute to some of the associated pathophysiology, such as cardiovascular instability.

SYNTHESIS AND CONCLUSIONS

Imaging studies of brain changes in major depression and other mood and anxiety disorders are showing that changes in volume of structures, such as hippocampus, prefrontal cortex, and amygdala, must be considered as part of the neurobiological consequences of these illnesses. Structural remodeling in these brain regions is im-

portant for human psychiatric disorders, because the altered circuitry is likely to contribute to impaired cognitive function and affect regulation.[2,6] Moreover, stress is widely acknowledged as a predisposing and precipitating factor in psychiatric illness.[20]

We have also seen how animal models are relevant to the study of human major depressive disorder in a number of ways. In the first place, they have led to the concept that structural changes occur in the depressed brain, and they continue to fuel studies of how the human brain changes structurally in depression and related psychiatric disorders. Secondly, animal models are showing that the structural changes that occur with chronic stress appear to be reversible as long as the stress is terminated in time. This suggests the optimistic possibility that brain changes in major depression and other psychiatric disorders may be treatable if we can find the right agents or therapies and intervene in time. Thirdly, reversible or not, the effects of chronic stress may predispose to greater vulnerability to adverse consequences from other insults. Finally, the systemic manifestations of the imbalances of hormonal and other mediators generated by chronic psychiatric disorders affect the metabolic, immune, and cardiovascular systems, leading to systemic disorders that further impair many of those who suffer from chronic depressive illness and add to the costs of healthcare.

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