INTRODUCTION

Protective and Damaging Effects of Stress Mediators: The Good and Bad Sides of the Response to Stress

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STRESS IS A CONDITION of human existence and a factor in the expression of disease. A broader view of stress is that it is not just the dramatic stressful events that exact their toll but rather the many events of daily life that elevate activities of physiological systems so as to cause some measure of wear and tear. This wear and tear is called "allostatic load," and it reflects the impact not only of life experiences that are stressful, but also of genetic constitution; individual habits reflecting items such as diet, exercise, and substance abuse; and developmental experiences that set life-long patterns of behavior and physiological reactivity.[1]

Thus, lifestyle is as important a factor in allostatic load as are the experiences that we classify as stressful, and the effects of allostatic load on body shape, size and function are often gradual and almost imperceptible as they develop over months and years. In many cases, the physiological and behavioral aspects of lifestyle and stress interact with each other, such as when we grab a bag of potato chips or smoke a cigarette while experiencing psychological stress due to an important event or deadline.

Allostasis, a term coined by Sterling and Eyer[2] means literally "achieving stability, ie, homeostasis, through change." It reflects the active process of coping physiologically and behaviorally with challenges to the individual. Hormones associated with allostasis and allostatic load protect the body in the short-run and promote adaptation, but in the long run allostatic load causes changes in the body that lead to disease. These hormones include the so-called "stress hormones" of the adrenal medulla and adrenal cortex, the catecholamines, and glucocorticoids. However, many other cellular mediators in tissues, such as excitatory amino acid neurotransmitters, as well as other circulating hormones, show similar patterns of promoting short-term adaptation but promoting pathophysiology if they are overproduced or not properly regulated.

This general principle can be illustrated for the immune system and brain. Acute stress actually enhances the ability of the immune system to respond to pathogens and it does so by facilitating the "trafficking" of immune cells to tissue where they are needed. Adrenal steroids and catecholamines act as mediators of this trafficking, in addition to their role in enhancing the delayed-type hypersensitivity (DTH) response.[3-5] In contrast, chronic stress dampens the immune response as well as the trafficking response to acute stress, and elevated glucocorticoids at high doses mimic this effect.[6,7] Thus, both the protective and damaging effects of adrenal steroids are seen in the immune system.

The brain is a key player in the response to stress and in determining the degree of allostatic load. The brain is also the interpreter of what is or is not a threat to the individual, based on prior experiences and developmental history, in addition to genotype. Not only does the brain control hormone release, it also controls behaviors that can either get the individual out of trouble, or the opposite.[1] In the short run, glucocorticoids and catecholamines secreted in response to stress enhance the formation of memories for emotionally laden events.[8,9] However, repeated stress causes longer-lasting effects that include atrophy of neurons in the hippocampus, a key brain region for declarative, episodic, and spatial memory.[10,11] Remodeling of hippocampal structure with repeated stress involves suppression of ongoing neurogenesis in the dentate gyrus, as well as the shortening of dendritic trees in the Ammon's horn and dentate gyrus.[10]

The human hippocampus atrophies not only in dementia but also in normal aging, Cushing's disease, depressive illness and post-traumatic stress disorder.[12,13] Some of these effects are also reversible, and preventable with certain treatments (eg, in Cushing's disease[14]); however, extremely prolonged and severe stress causes loss of nerve cells within the hippocampus.[11] One challenge is to determine whether agents that prevent stress-induced atrophy in animal brains are effective in treating human hippocampal atrophy and whether these agents can arrest the progression of degenerative brain changes toward permanent dementia.

The vulnerability of many systems of the body to stress is influenced by experiences early in life. In animal models, unpredictable prenatal stress causes increased emotionality and increased reactivity of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system, and these effects last throughout the lifespan.[15] Postnatal handling in rats, a mild stress involving brief daily separation from the mother, counteracts the effects of prenatal stress and results in reduced emotionality and reduced reactivity of the HPA axis and autonomic nervous system.[16-18] Taken together, these types of studies provide a basis in a relatively simple animal model for study of human conditions in which early life events such as parental loss, neglect, and even abuse in childhood exert long-lasting influences on behavior, emotionality and health[19-21] and in which nurturing and social support can ameliorate at least some of the negative outcomes of inexperienced or poor parenting.[22-24]

For prenatal stress and postnatal handling, once the emotionality and the reactivity of the adrenocortical system are established by events early in life, it is the subsequent actions of the HPA axis in adult life, as discussed above, that are likely to

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contribute to the rate of brain and body aging. Rats with increased HPA reactivity show early decline of cognitive functions associated with the hippocampus,[25] as well as increased propensity to self-administer drugs such as amphetamine and cocaine.[26,27] In contrast, rats with a lower HPA reactivity as a result of neonatal handling have a slower rate of cognitive aging and a reduced loss of hippocampal function.[28-30] Thus, life-long patterns of adrenocortical function, determined by early experience, contribute to rates of brain aging, at least in experimental animals.

Evidence for a human counterpart to the story of individual differences in rat HPA activity and hippocampal aging is very limited. Individual differences in human brain aging that are correlated with cortisol levels have been recognized in otherwise healthy individuals followed over a number of years.[31-33] In the most extensive investigation, healthy elderly subjects were monitored over a 4-year period. Those who showed a significant and progressive increase in cortisol levels, during yearly examinations, and who had high basal cortisol levels in year 4, showed deficits on tasks measuring explicit memory and selective attention compared to subjects with either decreasing cortisol levels over 4 years or increasing basal cortisol but moderate current cortisol levels.[31] Magnetic resonance images showed a hippocampus that was 14% smaller than that of age-matched controls who did not show progressive cortisol increases and were not cognitively impaired.[32] In these studies, the influence of early life events was not investigated. Such studies are very much needed but are clearly difficult because of the problems of accurately accessing early life events through retrospection.

Among the most potent of stressors throughout life are those arising from competitive interactions between animals of the same species, leading to the formation of dominance hierarchies.[34] Psychosocial stress of this type not only impairs cognitive function of lower ranking animals, but it can also promote disease (eg, atherosclerosis) among those vying for the dominant position.[1,10,35] Social ordering in human society is also associated with gradients of disease, with an increasing frequency or mortality and morbidity as one descends the scale of socioeconomic status that reflects both income and education.[36] Although the causes of these gradients of health are very complex, they are likely to reflect, with increasing frequency at the lower end of the scale, the cumulative burden of coping with limited resources and negative life events and the allostatic load that this burden places on the physiological systems involved in coping and adaptation.[36,37]

Articles in this issue of *Metabolism* summarize various aspects of the neurobiology, endocrinology, and psychological, clinical, and economic aspects of stress and allostatic load. Noble discusses the diagnosis of stress, while Duhault reports on current strategies for stress prevention and management. Kalia discusses the economic costs of stress and how they are estimated. Miller and O'Callaghan address the neuroendocrine processes involved in stress and allostatic load, with particular emphasis on corticotropin-releasing factor (CRF or CRH) and glucocorticoids, while Nicolaidis discusses the "taxonomy of stress" in terms of the different patterns of response of the classical stress mediators, glucocorticoids and catecholamines, as well as other hormones to different types of stressors. Plante provides an analysis of the vascular responses to stress in the normal and hypertensive state, and Wurtman presents an overview of the links between the adrenal medulla and adrenal cortex in the production of epinephrine. Hamet and Tremblay discuss the genetic aspects of hypertension and describe initial results of a quantitative trait locus approach to study markers related to hypertension and stress in inbred rat strains. Van-Itallie discusses stress as a risk factor for serious illness and focuses on post-traumatic stress disorder as an example. His article, along with that of Miller and O'Callaghan, develops the theme of stress as it fits into the concepts of allostasis and allostatic load.

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