Development of the Cerebral Cortex: XIII. Stress and Brain Development: II

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In spite of their bad reputation, stress hormones have a protective as well as a damaging effect on the body. Whether the good or bad side of stress hormone action predominates depends on the time course of the hormonal stress response, as well as the body's exposure to stress hormones.

Let us consider some examples. Glucocorticoids are so named because of their ability to promote conversion of protein and lipids to usable carbohydrates. In the short run, this serves the body well 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, another way of regulating energy, and to increase locomotor activity and food-seeking behavior. This serves us well after running two miles, but it is not beneficial when we grab a bag of potato chips while cramming for an exam or writing a grant application. Inactivity and lack of energy expenditure

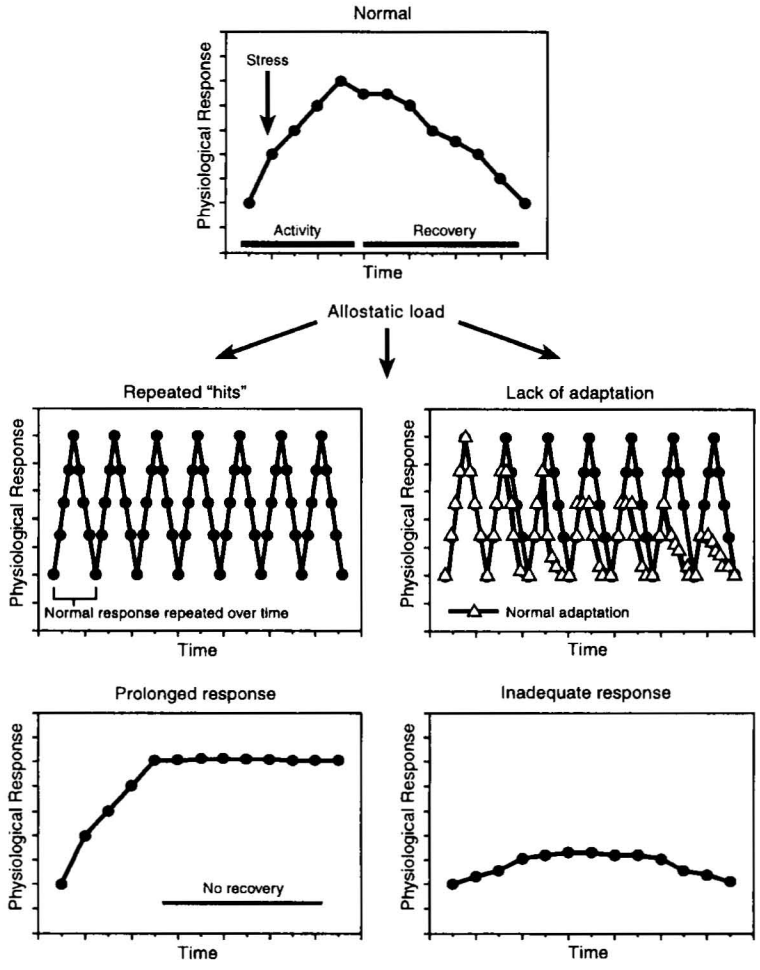

Fig. 1 The top panel illustrates the normal allostatic response, in which a response is initiated by a stressor, sustained for an appropriate interval, and then turned off. The remaining panels illustrate four conditions that lead to allostatic load: repeated "hits" from multiple stressors; lack of adaptation; prolonged response due to delayed shutdown; and inadequate response that leads to compensatory hyperactivity of other mediators (e. g., inadequate secretion of glucocorticoids, resulting in increased concentrations of cytokines that are normally counterregulated by glucocorticoids). From McEwen BS (1998), Protective and damaging effects of stress mediators. *N Engl J Med* 338:171–179.

creates a situation in which chronically elevated glucocorticoids can 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. This combination of hormones also contributes to the formation of atherosclerotic plaques in the coronary arteries.

For the heart, we see a similar paradox. Catecholamines and the combination of glucocorticoids and insulin can have dangerous effects on the body, besides their important short-term adaptive roles. 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. Our blood pressure rises and falls throughout the day as physical and emotional demands change, providing adequate blood flow as needed. Yet elevated blood pressure also promotes the generation of atherosclerotic plaques, particularly when combined with a supply of cholesterol and lipids and oxygen free radicals that damage the coronary artery walls. β-Adrenergic receptor blockers are known to inhibit this cascade of events and to slow down the atherosclerosis produced in dominant male cynomolgus monkeys in an unstable dominance hierarchy.

In the brain, strong emotions frequently lead to "flashbulb" memories—e.g., where we were when we heard of John Kennedy's assassination or Princess Diana's fatal accident; or remembering the location and events associated with a very positive life-event, like proposing marriage or receiving a promotion or award. Both catecholamines acting via β-receptors and glucocorticoids acting via intracellular hormonal receptors play an important role in establishing these long-lasting memories, and a number of brain structures participate along with the autonomic nervous system. The amygdala plays an important role in this type of memory. It is aided in its efforts by the autonomic nervous system, which picks up a signal from circulating adrenaline, and by the hippocampus, which helps us remember "where we were and what we were doing" at the time the amygdala was turned on in such a powerful way.

The paradox for the brain comes when there is repeated stress over many days or when glucocortical levels remain high because of adrenal overactivity or poor regulation of the stress response. The result is atrophy of pyramidal neurons in the hippocampus and shutdown of ongoing neurogenesis in the dentate gyrus. After very prolonged and severe stress, pyramidal neurons may actually die. Through these processes, the hippocampus atrophies. This can be seen in the human brain by magnetic resonance imaging.

Thus protection and damage are the opposite and seemingly unavoidable extremes of the hormonal stress response. What are the characteristics of the overactivity of the stress hormone axis that leads to pathophysiology and damage? Figure 1 presents a number of alternative patterns in the response to stress and illustrates what is called *allostatic load*. Allostasis refers to the process of adaptation to acute stress, involving the output of stress hormones that act in the ways described above to restore homeostasis in the face of a challenge. Allostatic load refers to the inefficient operation of the stress hormone response system, which must be turned on and then turned off again after the stressful situation is over (see top panel in Fig. 1).

As the top left of the four panels in Figure 1 illustrates, the stress hormone response may simply be turned on a lot by many different events. This is what happens with "chronic stress," and the negative consequences of overexposure to stress hormones results in the pathophysiology and wear and tear described above. People who have had excessive stress in their lives, as measured by multiple periods of poverty-level income, show earlier aging and decline of both physical and mental functioning.

There are circumstances in which the number of stressful events may not be excessive but in which the body fails to manage the hormonal stress response. These are illustrated in the 3 remaining panels in Figure 1. The top right panel illustrates a failure to habituate to repeated stressors of the same kind. Measurement of cortisol in a repeated public-speaking challenge has revealed individuals who do not habituate, and these individuals, who lack self-confidence and self-esteem, are undoubtedly overexposing their bodies to stress hormones under many circumstances in daily life that do not overtly disturb other individuals.

The bottom left panel of Figure 1 refers to failure to turn off each stress response efficiently. One example is individuals with two parents with hypertension, who show prolonged elevation of blood pressure after a psychological stressor. Another example is the hypersecretion of cortisol in the evening in people who have been sleep-deprived, as well as in depressed individuals. In the latter case, loss of bone mineral density has been reported.

The bottom right panel of Figure 1 describes a situation in which the hormonal stress response is inadequate to the needs of the individual genotype, resulting in excessive activity of other allostatic systems such as the inflammatory cytokines, which are normally contained by elevated levels of cortisol and catecholamines. The Lewis rat illustrates this condition, having less corticosterone than the virtually syngenic Fischer rat. Lewis rats are vulnerable to inflammatory and autoimmune disturbances that are not found in Fischer rats. Comparable human disorders involving lower-than-needed cortisol include fibromyalgia and chronic fatigue syndrome.

Whether stress hormones cause protection or damage is related to the dynamics of the hormonal stress response. Differences in hormonal dynamics and allostatic load may explain gradients of morbidity and mortality that are seen across the range of income and education referred to as "socioeconomic status" and that account for striking differences of health between rich and poor.

WEB SITES OF INTEREST

http://www.cyberounds.com/whats_new/
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ADDITIONAL READINGS

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Erratum

In the article "Diagnostic Utility of Two Commonly Used ADHD Screening Measures Among Special Education Students" by Regina Bussing et al. (Vol. 37, pp. 74–82), several values in Table 3 were incorrect. The correct values are as follows:

- PVN for ASQ-65 in boys is .72 and the corresponding se is .037
- PVN for ASQ-70 in boys is .69 and the corresponding se is .035; the significance indicator was correct as placed
- PVP for ASQ-70 in boys is .74 and the corresponding se is .046

The authors regret the errors.