Cortisol

Cortisol is a powerful, naturally-occurring steroid hormone produced in the adrenal glands situated atop each kidney. It is released in a diurnal cycle with levels peaking around 9:00 a.m. and dropping throughout the day until around midnight. Its release is also increased in response to stress. Under normal physiologic and environmental conditions cortisol functions to control blood sugar through a variety of mechanisms, to suppress the immune system, and to aid in the metabolism of fats, proteins, and carbohydrates.[1] In addition to its important role in normal daily functioning, cortisol is a key player in the stress response. In response to a physical or psychological threat (stressor), cortisol levels surge to provide the energy and substrate necessary to cope with stress-provoking stimuli or escape from danger.[2,3]

Cortisol also may facilitate the consolidation of fear-based memories for future survival and *avoidance* of danger.[4] This carefully orchestrated yet near-instantaneous sequence of hormonal changes and physiological responses happen so quickly that people aren't even aware of them. And while this stress-induced increase in cortisol secretion is adaptive in the short-term, excessive or prolonged cortisol secretion may have crippling, mal-adaptive effects, both physically and psychologically.[5] Under *ab*normal (stressful) conditions, or with prolonged exposure, cortisol can lead to a variety of pathological processes including muscle-wasting,[6] osteoporosis,[7] delayed wound-healing times,[8] remodeling of the architecture of neurons in the central nervous system (CNS)[9], anxiety, depression, and addiction.[10]

What Do We Mean by "Stress?"

Stress and stressful experiences have long been implicated in the origin and pathophysiology of chronic physical and mental health conditions that now pose a great threat to public health.[11] Fundamentally we can classify a stressful experience as "good", "tolerable", or "toxic" depending on the degree to which a person has control over a given stressor and has the resources and support systems in place for coping with it.[12,13]

"Good" stress refers to the experience of taking a risk, rising to the challenge, and feeling rewarded by a positive outcome; it can be rewarding and pleasant, or even exciting, providing positive stimuli to the individual for emotional and intellectual growth and development.[14]

"Tolerable" stress refers to those experiences or situations where 'bad' things happen, but the person with healthy brain architecture and a sufficient psychosocial support system is able to cope.

Finally, "Toxic" stress refers to situations where 'bad' things happen to an individual without the requisite resources to cope with whatever is happening. With toxic stress, the inability to cope is likely to have adverse effects on behavior and physiology, and this will result in a higher degree of allostatic overload.

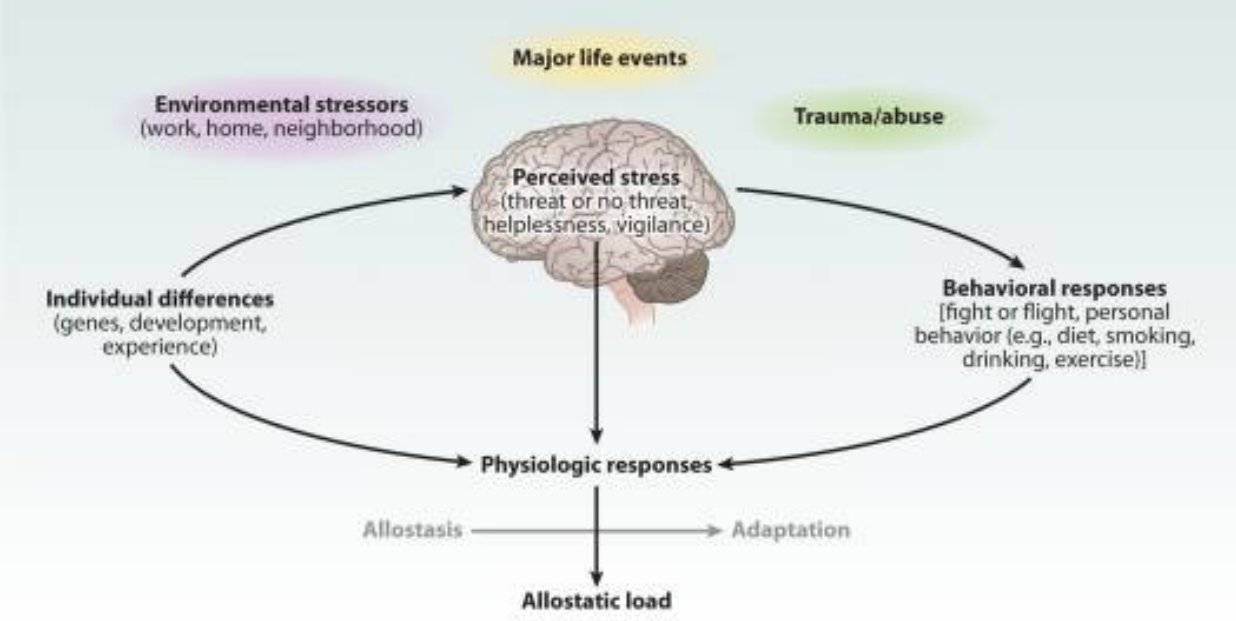
Allostasis and Allostatic Overload

Allostasis is the dynamic, near-instantaneous reactions that occur via mediators, both systemic and molecular, in response to a continually changing input of sensory stimuli, both from the internal and external milieu in order to promote adaptation. But these same mediators have biphasic effects and can also promote pathophysiology when overused or when their activity is out of balance with each other (*allostatic overload*). Adaptation and protection via

allostasis and wear-and-tear on the body and brain via allostatic overload are the two of the many contrasting sides of the physiology involved during the challenges of daily life.

Allostatic systems promote adaptation to stressful experiences and are generally most useful when rapidly mobilized and terminated. When they are prolonged or not terminated promptly, allostatic systems undermine mental and physical health—primarily because of their effects on brain plasticity (see below).[15]

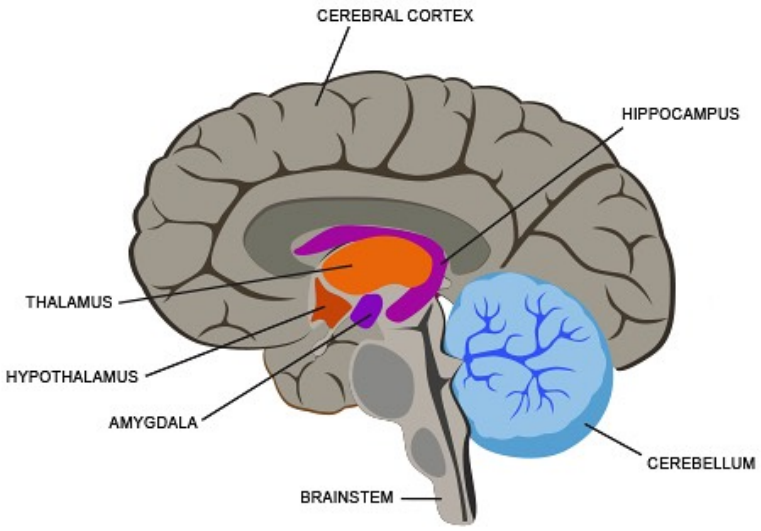
An important aspect of allostasis and allostatic load is the notion of anticipation. Here, anticipation implies psychological states, such as apprehension, worry, and anxiety, as well as cognitive preparation for a forthcoming event. Anticipation arising from neural activity within the brain can drive the output of allostatic biomediators, and it is likely that states of prolonged anxiety and anticipation can result in allostatic load.[16]



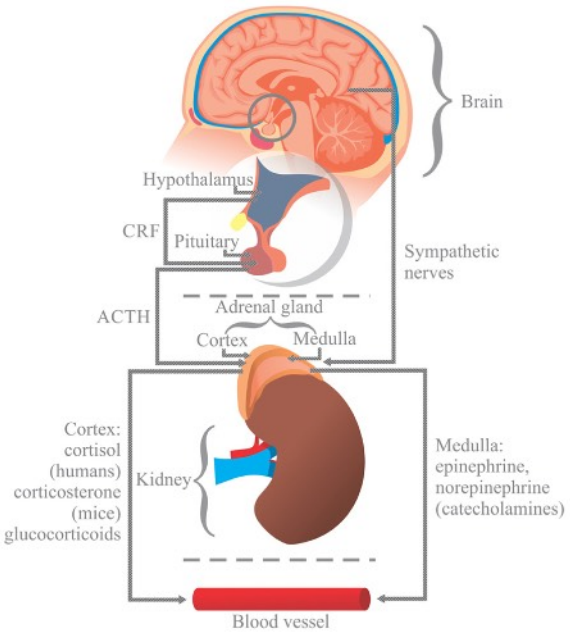
Central role of the brain in allostasis and the behavioral and physiological response to stressors.

The Acute Stress Response

The stress response begins in an area of the brain known as the amygdala. (see illustration). The amygdala then signals the brain stem to initiate the release of epinephrine and



norepinephrine from the adrenal gland.[17,18] Perceiving danger, the amygdala simultaneously signals a region of the brain called the the hypothalamus to release corticotropin-releasing hormone (CRH), which travels to the pituitary gland, triggering the release of adrenocorticotropic hormone (ACTH). This hormone travels to the adrenal glands, prompting them to release cortisol. This, along with the release of epinephrine and norepinephrine from the sympathetic nervous system (SNS), acts to get us revved-up and placed on high alert.

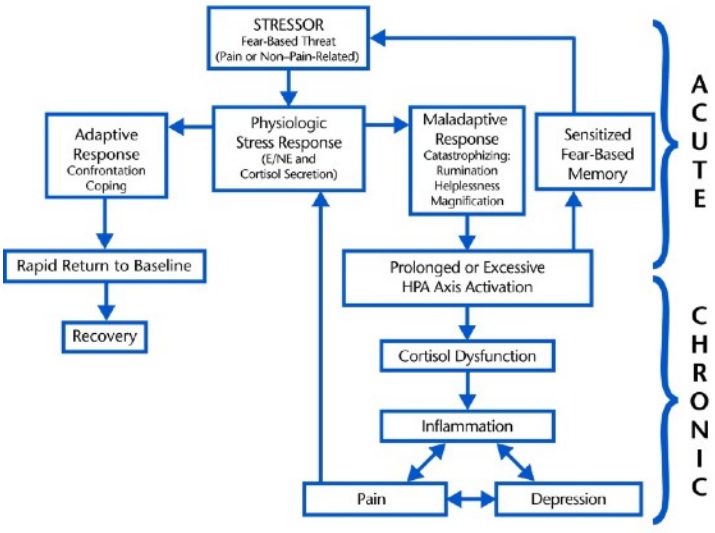


Under normal conditions, cortisol secretion during an acute stress response serves to mobilize glucose reserves for energy, inhibit pain, divert blood from non–vital organ systems, and promote an adaptive fight-or-flight response.[19] Additionally, stress-induced cortisol secretion may facilitate the formation of a fear-based memory conditioned to elicit a sensitized fight-or-flight response to promote survival and avoidance of future threat.[20]

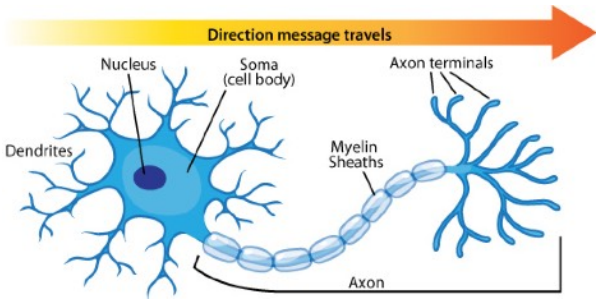
We emphasize that the brain is the central mediator of *and* (*a*) determines what is threatening, and hence stressful, to the individual; (*b*) regulates the physiological, behavioral, cognitive, and emotional responses that an individual will deploy in order to cope with a given stressor; and (*c*) changes in its plasticity both adaptively and maladaptively as a result of coping with stressful experiences.

Chronic Activation of The Acute Stress Response

As previously discussed, chronic bombardment of the CNS from repeated or prolonged stressors, or even *perceived* stressors/threats,[21] and hence chronically high levels of cortisol, place the brain at risk for neuronal remodeling and dysfunction,[22] as well as deficits in cognitive performance. In humans at least, the stress responses may be inappropriately and chronically activated by rumination and worry (anticipatory stress). This stress-related cortisol secretion is likely to contribute to the consolidation of fear-based emotional memories that are readily recruited by nonthreatening stimuli and conditioned to reactivate the stress response.



Discussion



The brain is the central organ of stress and adaptation. It regulates and responds to the mediators of allostasis, including cortisol, which are normally involved in adaptation but which, when dysregulated and overused, lead to allostatic load.

Cortisol is a powerful and important steroid hormone that plays a key role in the stress response, but chronic overstimulation of the CNS via the stress response can alter the basic structural architecture of individual neurons.[22] The discussion of this topic is outside the scope of this article, but nonetheless warrants further investigation regarding not only the deleterious effects of chronic overstimulation from high circulating levels of cortisol, but also into the exciting world of rehabilitative neuroplasticity; the *positive* structural adaptations at the level of the neuron that reflect an increase in healthy stimulation and a decrease in negative (stressful) stimuli. Reversibility of maladaptive forms of stress-related brain plasticity is possible, and this reversibility may underpin many forms of future treatment.

References

[1] Hoehn K, Marieb EN (2010) *Human Anatomy and Physiology.* San Francisco: Benjamin Cummings. ISBN 978-0-321-60261-9.

[2] Blackburn-Munro G, Blackburn-Munro R. Pain in the brain: are hormones to blame? Trends Endocrinol Metab. 2003;14:20–27.

[3] Jankord R, Herman JP. Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. Ann NY Acad Sci. 2008;1148:64–73.

[4] Hannibal KE, Bishop MD. Chronic stress, cortisol dysfunction, and pain: a psychoneuroendocrine rationale for stress management in pain rehabilitation. Phys Ther (2014) 94:1816–25. 10.2522/ptj.20130597

[5] McEwen BS. Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators. Eur J Pharmacol. 2008;583:174–185

[6] Simmons PS, Miles JM, Haymond MW (February 1984). "Increased proteolysis. An effect of increases in plasma cortisol within the physiologic range". The Journal of Clinical Investigation. **73** (2): 412-20. PMID 6365973

[7] Chyun YS, Dream BE, Raisz LG (February 1984). "Cortisol decreases bone formation by inhibiting periosteal cell proliferation". *Endocrinology*. **114** (2):477-80. PMID 6690287

[8] Ebrecht M, Hextall J, Kirtley LG, Taylor A, Dyson M, Weinman J: Perceived stress and cortisol levels predict speed of wound healing in health male adults. Psychoneuroendocrinology. 2004, 29: 798-809. 10.1016/S0306-4530(03)00144-6.

[9] The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. *McEwen BS, Morrison JHNeuron. 2013 Jul 10; 79(1):16-29.*

[10] https://www.health.harvard.edu/staying-healthy/understanding-the-stress response

[11] Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. JAMA. 2007;298:1685–88. [PubMed] [Google Scholar]

[12] Lazarus RS, Folkman S, editors. Stress, Appraisal and Coping. New York: Springer-Verlag; 1984. [Google Scholar]

[13] Knudsen EI, Heckman JJ, Cameron JL, et al. Economic, neurobiological, and behavioral perspectives on building America's future workforce. Proc Natl Acad Sci USA. 2006;103:10155–62. [PMC free article] [PubMed] [Google Scholar]

[14] Dorn LD, Chrousos GP. The endocrinology of stress and stress system disorders in adolescence. Endocrinol Metab Clin North Am 1993;22:685-700.

[15] McEwen B.S., Gianaros P.J. Stress- and allostasis-induced brain plasticity. Annu. Rev. Med. 2011;62:431–445. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[16] Schulkin J, McEwen BS, Gold PW. Allostasis, amygdala, and anticipatory angst. Neurosci Biobehav Rev. 1994;18:385–96. [PubMed] [Google Scholar]

[17] Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res. 2002;53:865–871. [PubMed] [Google Scholar]

[18] Sorrells SF, Caso JR, Munhoz CD, Sapolsky RM. The stressed CNS: when glucocorticoids aggravate inflammation. Neuron. 2009;64:33–39. [PMC free article] [PubMed] [Google Scholar]

[19] Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology. 2000;25:1–35. [PubMed] [Google Scholar]

[20] 20 Hartley CA, Phelps EA. Changing fear: the neurocircuitry of emotion regulation. Neuropsychopharmacology. 2010;35:136–146. [PMC free article] [PubMed] [Google Scholar]

[21] Ebrecht M, Hextall J, Kirtley LG, Taylor A, Dyson M, Weinman J: Perceived stress and cortisol levels predict speed of wound healing in health male adults. Psychoneuroendocrinology. 2004, 29: 798-809. 10.1016/S0306-4530(03)00144-6.

[22] The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. McEwen BS, Morrison JH, Neuron. 2013 Jul 10; 79(1):16-29.