Sleep Deprivation and Circadian Disruption

Stress, Allostasis, and Allostatic Load

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KEYWORDS

• Sleep deprivation • Hippocampus • Allostasis • Allostatic load • Glycogen • Oxidative stress
• Pro-inflammatory cytokines • Circadian disruption

KEY POINTS

- Allostatic load/overload refers to the cumulative wear and tear on body systems caused by too much stress and/or inefficient management of the systems that promote adaptation through allostasis.
- Circadian disruption is a broad problem that alters allostasis and elevates allostatic load, affecting brain and body systems. Sleep deprivation is an all-too-common example of a process that includes circadian disruption.
- Even a few days of sleep deprivation or circadian misalignment in young healthy volunteers have been reported to increase appetite and caloric intake, increase levels of pro-inflammatory cytokines, decrease parasympathetic and increase sympathetic tone, increase blood pressure, increase evening cortisol levels, as well as elevate insulin and blood glucose.
- Chronic circadian disruption and reduced sleep time are associated with elevated cortisol, increased obesity, and reduced volume of the temporal lobe.
- Mood disorders involve disrupted circadian rhythmicity and altered sleep-wake patterns; yet, acute sleep deprivation can have rapid antidepressant effects and manipulating the timing of the secretion or exogenous administration of melatonin can be beneficial in mood disorders.
- Repeated stress in animal models causes brain regions involved in memory and emotions, such as hippocampus, amygdala, and prefrontal cortex, to undergo structural remodeling with the result that memory is impaired and anxiety and aggression are increased. Structural and functional MRI studies in depression and Cushing disease, as well as anxiety disorders and in air crews with jet lag, provide evidence that the human brain may be similarly affected.
- Brain regions such as the hippocampus are sensitive to glucose and insulin, and both type I and type II diabetes are associated with cognitive impairment and (for type II diabetes) an increased risk for Alzheimer disease. Insofar as poor sleep and circadian disruption also exacerbate metabolic dysregulation as well as contribute to other aspects of physiologic dysregulation, they must be considered contributors to risk for dementia.
- Animal models of chronic sleep deprivation indicate that memory is impaired along with depletion of glycogen stores and increases in oxidative stress and free-radical production.

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INTRODUCTION

Anecdotally, there can be little doubt that sleep plays a role in maintaining a good mood and cognitive acuity. Sleep deprivation one night followed by "getting a good night's sleep" on the next clearly impacts neurobehavioral function as well as promotes physiologic balance and resilience. These subjective impressions are supported by numerous laboratory studies of endocrine function and metabolism as well as from investigations of sleep deprivation effects on cognitive and neural function, including research on the brain that shows a variety of substantial changes resulting from sleep restriction, with reversal after recovery sleep. Similarly, being "out of phase" with local time, be it from a week of nightshift work following a week of dayshift work, or transmeridian air travel across multiple time zones, demonstrates that there are both neural and physiologic effects of internal circadian (daily) time being misaligned with external environmental time. This article reviews selected aspects of the current state of knowledge in these areas and then evaluates what is known using the model of allostasis and allostatic load that emphasizes the "wear and tear" on the brain and body from coping with stress.

ALLOSTASIS AND ALLOSTATIC OVERLOAD

The maintenance of homeostasis, defined as those aspects of physiology that must remain stable to keep us alive (eg, oxygen tension, body temperature, pH), is an active process requiring coordinated action of many different systems, including the autonomic nervous system and neuroendocrine and immune systems. This active process is called "allostasis" or "maintaining stability through change."[1–3] Allostatic mediators work as a nonlinear, sometimes reciprocating, network (Fig. 1), meaning that too much or too little of each mediator can perturb the entire network, leading to harmful consequences. Take for example the relationship between cytokines and the glucocorticoids. Pro-inflammatory cytokines stimulate the production of cortisol, which then suppresses inflammatory cytokine production.[4,5] Similarly, increased activity of the sympathetic nervous system increases pro-inflammatory cytokine production, whereas parasympathetic activity has the opposite effect.[6,7] This balance is particularly important, as during an infection, the pro-inflammatory response that is essential to mounting an immune defense is normally contained by cortisol and also by parasympathetic activity.[4,6] Inadequate containment can lead to septic shock and death. Treatment with cortisol, or elevation of parasympathetic activity, is a pathway that can reduce the exaggerated inflammatory response.[4] However, at the opposite extreme, too much cortisol can suppress pro-inflammatory responses, thus compromising immune defenses.[4,8]

Allostatic overload, which is wear and tear produced by imbalances in the mediators of allostasis, is perfectly illustrated by these 2 examples: too much or too little activity of certain mediators of allostasis.[9] Other examples of allostatic overload include conditions such as hypertension, atherosclerosis, diabetes, and the metabolic syndrome as well as stress-induced remodeling in brain regions that support memory, executive function, and anxiety.[3,10] One of the key mediators

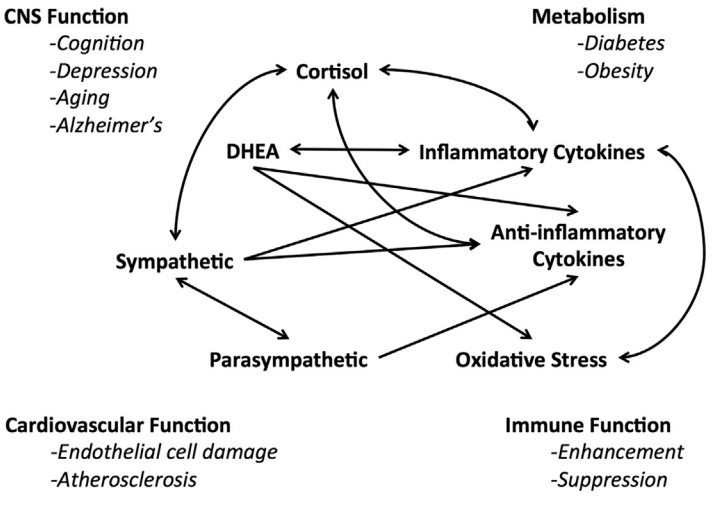

Fig. 1. Nonlinear network of mediators of allostasis involved in the stress response. Arrows indicate that each system regulates the others in a reciprocal manner, creating a nonlinear network. Moreover, there are multiple pathways for regulation (eg, inflammatory cytokine production is negatively regulated via anti-inflammatory cytokines as well as via parasympathetic and glucocorticoid pathways), whereas sympathetic activity increases inflammatory cytokine production. Parasympathetic activity, in turn, contains sympathetic activity. CNS, central nervous system; DHEA, dehydroepiandrosterone. (*Adapted from* Karatsoreos IN, McEwen BS. Psychobiological allostasis: resistance, resilience and vulnerability. Trends Cogn Sci 2011;15:576–84; with permission.)