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Sleep deprivation as a neurobiologic and physiologic stressor: allostasis and allostatic load

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Abstract

Sleep has important homeostatic functions, and sleep deprivation is a stressor that has consequences for the brain, as well as many body systems. Whether sleep deprivation is due to anxiety, depression, or a hectic lifestyle, there are consequences of chronic sleep deprivation that impair brain functions and contribute to allostatic load throughout the body. Allostatic load 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. Chronic sleep deprivation in young healthy volunteers has been reported to increase appetite and energy expenditure, increase levels of proinflammatory cytokines, decrease parasympathetic and increase sympathetic tone, increase blood pressure, increase evening cortisol levels, as well as elevate insulin and blood glucose. 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 magnetic resonance imaging studies in depression and Cushing's disease, as well as anxiety disorders, provide evidence that the human brain may be similarly affected. Moreover, brain regions such as the hippocampus are sensitive to glucose and insulin, and both type 1 and type 2 diabetes mellitus are associated with cognitive impairment and (for type 2 diabetes mellitus) increased risk for Alzheimer's disease. 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. Taken together, these changes in brain and body are further evidence that sleep deprivation is a chronic stressor and that the resulting allostatic load can contribute to cognitive problems, which can, in turn, further exacerbate pathways that lead to disease.

1. Introduction

From the personal experience of sleep deprivation and then subsequently "getting a good night's sleep," there can be little doubt that sleep plays a role in maintaining a good mood and cognitive acuity, as well as in promoting physiologic balance and resilience. These impressions are supported by studies of endocrine function and metabolism, as well as from investigations of sleep deprivation effects on cognitive and neural function. This includes research on the brain that shows a variety of substantial changes resulting from sleep restriction, with reversal after recovery sleep. This article reviews selected aspects of the current state of knowledge in this area and then evaluates what is known using the model of allostasis and allostatic load, which emphasizes the "wear and tear" on the brain and body from coping with stress.

2. Allostasis and allostatic overload

The maintenance of homeostasis is an active process that requires the output of mediators such as those of the autonomic nervous system, and the neuroendocrine and immune systems.

This process is called "allostasis," or "maintaining homeostasis through change" [1-3]. The mediators of allostasis work as a nonlinear network (Fig. 1), meaning that too much or too little of each mediator can have harmful consequences by perturbing the entire network. This is because the mediators reciprocally regulate each other. For example, proinflammatory cytokines stimulate the production of cortisol, which suppresses inflammatory cytokine production [4,5]. Sympathetic nervous system activity increases proinflammatory cytokine production, whereas

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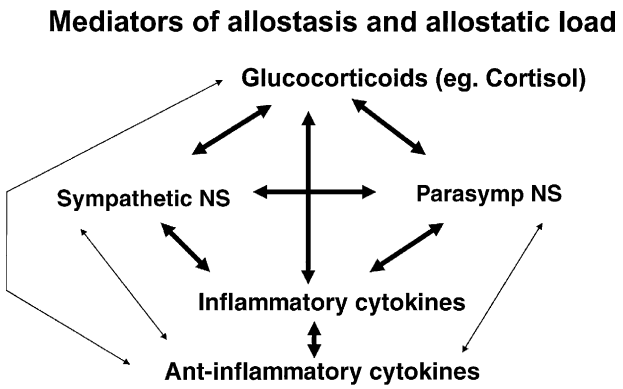

Fig. 1. Nonlinear network of mediators of allostasis involved in the stress response. Arrows indicate that each system regulates the others in a reciprocal manner, creating a nonlinear network. Moreover, there are multiple pathways for regulation; for example, inflammatory cytokine production is negatively 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.

parasympathetic activity has the opposite effect [6,7]. During an infection, the proinflammatory response that is essential to mounting an immune defense is normally contained by cortisol and also by parasympathetic activity [4,7]. Yet, inadequate containment can lead to septic shock and death, and treatment with cortisol and elevation of parasympathetic activity are 2 pathways to reducing the excess inflammatory response [4]. At the opposite extreme, too much cortisol can suppress the proinflammatory responses and compromise immune defenses [4,5].

These 2 examples—too much or too little activity of certain mediators of allostasis—illustrate allostatic overload [8], which is the wear and tear produced by imbalances in the mediators of allostasis. 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 [1,9]. Such changes in brain structure are seen in major depression and Cushing's disease.

In Cushing's disease, there are depressive symptoms that can be relieved by surgical correction of the hypercortisolemia [10]. Both major depression and Cushing's disease are associated with chronic elevation of cortisol that results in gradual loss of minerals from bone and abdominal obesity. In major depressive illness, as well as in Cushing's disease, the duration of the illness and not the age of the subjects predicts a progressive reduction in volume of the hippocampus, determined by structural magnetic resonance imaging [11,12]. Moreover, there are a variety of other anxiety-related disorders, such as posttraumatic stress disorder, in which atrophy of the hippocampus has been reported [13,14], suggesting that this is a common process reflecting chronic imbalance in the activity of adaptive systems, such as the hypothalamic pituitary axis (HPA), but also including endogenous neurotransmitters, such as glutamate.

3. Metabolic and hormonal responses to sleep deprivation

Sleep deprivation produces an allostatic overload that can have deleterious consequences. Sleep restriction to 4 hours of sleep per night increases blood pressure, decreases parasympathetic tone, increases evening cortisol and insulin levels, and promotes increased appetite, possibly through the elevation of ghrelin, a pro-appetitive hormone, and decrease in levels of leptin [15-17]. Proinflammatory cytokine levels are increased, along with performance in tests of psychomotor vigilance, and this has been reported to result from a modest sleep restriction to 6 hours per night [18]. Reduced sleep duration has been reported to be associated with increased body mass and obesity in the National Health and Nutrition Examination Survey (NHANES) study [19].

4. Neural responses to sleep deprivation

The brain is the master regulator of the neuroendocrine, autonomic, and immune systems, along with behaviors that contribute to unhealthy or healthy lifestyles, which, in turn, influence the physiologic processes of allostasis [1]. Alterations in brain function by chronic stress can therefore have direct and indirect effects on the cumulative allostatic overload. Allostatic overload resulting from chronic stress in animal models causes atrophy of neurons in the hippocampus and prefrontal cortex, brain regions involved in memory, selective attention, and executive function, and causes hypertrophy of neurons in the amygdala, a brain region involved in fear and anxiety, as well as aggression [20]. Thus, the ability to learn and remember and make decisions may be compromised by chronic stress and may be accompanied by increased levels of anxiety and aggression.

Although sleep deprivation has not yet been studied with respect to all of these aspects, there is increasing evidence not only for cognitive impairment resulting from sleep restriction, but also for altered levels of cytokines, oxidative stress markers, glycogen levels, and structural changes in the form of reduced dentate gyrus neurogenesis.

With respect to proinflammatory cytokines, interleukin-1β messenger RNA levels in brain are reported to increase after sleep deprivation by gentle handling and to be higher in daytime (during the normal sleep period in rodents) than in darkness (during the normal activity time for rodents) [21]. The actions of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [22,23] generate free radicals, and this process is involved in a feed forward loop with the generation of proinflammatory cytokines. Sleep deprivation in mice for 72 hours by the "flower pot" or platform method has been reported to increase oxidative stress in hippocampus as measured by increased lipid peroxidation and increased ratios of oxidized to reduced glutathione [24].

Sleep deprivation alters the level of glycogen, found predominantly in white matter, which is reported to decrease

by as much as 40% in rats deprived of sleep for 24 hours by novelty and gentle handling and reversed by recovery sleep [25,26]. It is noteworthy that glycogen in astrocytes is able to sustain axon function during glucose deprivation in central nervous system white matter [27].

Sleep deprivation in rats using a treadmill for 96 hours has been reported to decrease proliferation of cells in the dentate gyrus of the hippocampal formation by as much as 50% [28]. A similar effect has also been reported by keeping rats in a slowly rotating drum, but, here, again, there is a question of how much physical activity and physical stress may have contributed to the suppression of cell proliferation [29]. Nevertheless, sleep restriction by novelty exposure, a more subtle method, prevented the increased survival of new dentate gyrus neurons promoted by spatial training in a Morris water maze [30].

Indeed, with respect to memory and cognitive performance, there are numerous reports of impairments after sleep deprivation. For example, sleep deprivation by the platform (or flower pot) method resulted in impaired retention of passive avoidance memory, a context-dependent fear memory task [24], as well as impaired performance of spatial memory in the Morris water maze [31] and a reduction in long-term potentiation in the CA1 region of the hippocampus [32].

Sleep deprivation by gentle stimulation or novelty in the aftermath of contextual fear conditioning has been reported to impair memory consolidation [33]. Moreover, a 6-hour period of total sleep deprivation by novelty exposure impaired acquisition of a spatial task in the Morris water maze [34]. Furthermore, a 4-hour period of sleep deprivation by gentle stimulation impaired the late-phase long-term potentiation in the dentate gyrus 48 hours later, but had the opposite effect to enhance late-phase long-term potentiation in the prefrontal cortex [35].

Sleep deprivation has also been associated with increases in fighting behavior after deprivation of rapid eye movement sleep [36]; there is also a report of increased aggression in the form of muricide after phencyclidine administration during or after sleep deprivation [37]. These findings may be related to the finding of increased aggression among cage mates in rats subjected to 21 days of 6 hours per day of chronic restraint stress during the resting period when some sleep deprivation may occur [38]. Interestingly, a 12-hour sleep deprivation that is applied by using a slowly rotating drum, which minimizes physical stress but does produce locomotor activity, reversed the decreased open field behavior induced by a single social defeat [39].

5. Interpretation

Sleep deprivation studies in animals have involved radically different methods ranging from the flower pot or treadmill to the use of novelty or gentle stimulation for shorter time intervals. In spite of these different methods, which differ in the amount of physical stress, locomotor activity, and other variables, there is a consistent pattern of results for cognitive function, namely, impairment of learning and retention. For the brain, measures of proinflammatory cytokines have shown an increase from novelty/gentle handling, as well as an increase in oxidative stress from a more severe flower pot deprivation. Similarly, brain glycogen depletion is reported from sleep deprivation by gentle handling. Moreover, both neural cytokine messenger RNA levels and glycogen levels fluctuate during the day-night cycle, suggesting that such changes occur during the normal diurnal variation of sleep and activity and can grow in magnitude with more prolonged sleep deprivation.

The relatively mild and short durations of sleep restriction that have been used to impair memory and the prolongation of dentate gyrus neuron survival after spatial learning are also consistent with a close link of sleep to normal physiology and an exaggerated response during more extreme sleep deprivation. In spite of the convergence of evidence from disparate methods of sleep restriction, future research should attempt to develop a “dose response” for the effects of progressively increasing durations of sleep deprivation on systemic, for example, hormonal, and neural end points using the same methods of sleep deprivation, preferably those involving the novelty and gentle stimulation.

6. Conclusions

Sleep is believed to be a neural state during which consolidation of declarative memories are taking place [40]. Sleep deprivation, even for the course of the active period of the day, increases the homeostatic drive to sleep, with resulting changes in proinflammatory cytokines and glycogen levels. Moreover, relatively brief deprivation of sleep promotes an exacerbation of these processes with progressively more severe physiologic, neurobiologic, and behavioral consequences as the sleep deprivation is prolonged.

The long-term consequences of sleep deprivation constitute a form of allostatic load—with consequences involving hypertension, reduced parasympathetic tone, increased proinflammatory cytokines, increased oxidative stress, and increased evening cortisol and insulin. In addition, as noted above, reduced sleep is associated with increased risk for obesity, which means increased chances of cardiovascular disease and diabetes.

With diabetes there is also poorer cognitive function, as well as increased depression (see reference [41] and other articles in this volume) and increased risk for Alzheimer’s disease [42,43]. Depressive illness is almost universally associated with disturbed sleep [44]. Thus, there are linkages not only between the multiple, interacting mediators that are involved in allostasis and allostatic load, as summarized in Fig. 1, but also overlaps, that is, comorbidities, between the disorders, such as diabetes, hypertension, cardiovascular disease, and depression that are associated

with excessive stress and with the dysregulation of the systems that normally promote allostasis, or adaptation.

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