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Review Article
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Rehabilitation or Recovery Sleep: A Future Potential Therapeutic Target for Sleep Deprivation

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Abstract

Sleep is a period of relaxation and repair. During sleep, waste products of brain metabolism are removed. It plays central role in maintenance of physiological homeostasis and psychological balance. Sufficient sleep helps us think more clearly, complete complex tasks better and more consistently. One of the important function of sleep is to promote synaptic plasticity and neuronal recovery for proper brain functioning. Memory consolidation, brain growth and repair are other functions proposed for sleep. Problems related to sleep deprivation are being increased in today's modern society. Every day there seems to be twice as much work and half as much time to complete it, this results in a decrease in sleep or extended periods of wakefulness. Sleep deprived individuals may not have difficulty of verbal disturbances but research studies have shown that individuals have more difficulty in reacting well, to taking biological discussion and implementing the task with efficiency of action. Although day time performance due to sleep loss is experienced universally but in professionals such as paramilitary forces, army personals, who work under stressful conditions are more vulnerable to the sleep deprivation. These conditions become more stressful during emergencies and war because, after periods of extended wakefulness neurons may begin to malfunction, visibly affecting person's behavior. Rapid eye movement (REM) sleep plays a role in learning due to an activation of the hippocampus involved in encoding new memories. Many experiments have shown that the day after a good night's sleep, one may retain newly acquired knowledge or a newly learned skill more effectively. An enriched environment (EE) which is a complex combination of social, cognitive, and physical stimulation, improves learning and memory. Many changes such as increased brain weight, synaptic plasticity, gliogenesis, growth of dendritic spine as well as change in neurotransmitter content, up regulation of neuronal signaling molecules, neurotrophin levels and adult hippocampal neurogenesis have been reported.

Keywords: Sleep; Recovery; Wakefulness; Brain; Memory

Introduction

In this fast moving world, money is earned by sacrificing the basic needs of the body i.e. sleep. Sleep is one of the important needs like oxygen for survival and nutrition for health. Sufficient sleep helps us think more clearly, complete complex tasks better, more consistently. It is a state characterized by absence of consciousness, deferred sensory activity, and inactivity of voluntary muscles. In other words, it is a heightened anabolic state, accentuating the growth and rejuvenation of the immune, nervous, skeletal and muscular systems [1]. Sleep depends on two major factors: A circadian regulator and a homeostatic regulator. Homeostatic regulation means that sleep is delayed and often become more intense after extended waking, thus also called recovery sleep [2]. Xie et al. reported that during sleep, waste products of brain metabolism are removed; this is due to change in milieu of the brain's extracellular space between sleep and waking states [3]. Besides, sleep plays important role to promote synaptic plasticity and neuronal recovery for proper brain functioning [4]. Memory consolidation, brain growth and repair are other functions proposed for sleep [5].

The timing of sleep is organized by the circadian clock and sleep-wake homeostasis. The circadian clock works in association with the neurotransmitter adenosine, that inhibits wakefulness associated processes and cause sleepiness [6].

According to National sleep foundation and National Institutes of Health (NIH), National Center on Sleep Disorders Research and Office of Prevention, Education, and Control, USA 7-9 hours' sleep is necessary for adults or elderly.

Although sleep occupies approximately a one third of the human lifespan, the amount of time humans spend awake has increased over the years. Problems of sleep deprivation (SD) are being increased in today's modern society. SD results in either extended periods of wakefulness or a decrease in sleep over an extended period of time. Sleep deprived individuals though do not have difficulty of verbal disturbances but research studies have shown more difficulty in reacting well, to taking biological discussion and implementing them as well with efficiency of action. Day time effects due to sleep loss are experienced universally but in professionals belonging to paramilitary forces, army personals etc. who work under stressful conditions are more vulnerable to the sleep deprivation as conditions become more stressful during emergencies and war. After periods of extended wakefulness or reduced sleep, neurons may begin to malfunction, visibly affecting a person's behavior [7]. Sleep deprivation ensue mental fatigue, impaired learning, decision-making, epileptic attacks and heightened risk of migraine. Chronic or complete insomnia, which may ultimately, results in death [8].

It has been also evident that sleep deprivation is responsible for the induction and worsening of various neurological disorders. Sleep disorders include the circadian rhythm sleep disorders, narcolepsy, periodic limb movement disorder (PLMD), restless leg syndrome

(RLS), obstructive sleep apnea in which major pauses in breathing occur during sleep. Anxiety is also one of the most important neurobehavioral consequences of rapid eye movement (REM) sleep deprivation and total Sleep deprivation (both REM+NREM) [9,10]. SD also impairs cognition either by adversely affecting the encoding or initial learning of memories (referred to as acquisition) or by affecting memory consolidation. Studies in human subjects, suggested that insomnia markers are possible biomarkers for depression [11].

Recovery Sleep: The Potential Role of Enriched Environment

The old assumption that connections in the adult brain are rigid and no longer modifiable is luckily not true. Indeed, the brain is capable to adapt to new demands the whole life long, which is essential for learning processes and to adapt to our environment as a result of active training, passive exposure or if we suffer from a brain injury. That is what we call neuronal plasticity- the ability of the brain to adapt in response to modified inputs from the environment both structurally and functionally.

Environmental enrichment involves changes to an animal's home cage or secondary exploratory area which provide enhanced sensory, motor, cognitive and potentially social opportunities [12]. Rosenzweig et al. established EE (Environment enrichment) as a scientific concept (Figure 1) [13].

The purpose of EE is to provide possibilities for enhanced voluntary physical exercise, social interactions, multi-sensory and cognitive stimulation. Wakefulness and sleep deprivation are both characterized by increased activity of neuronal cells and increased consumption of ATP while in recovery sleep neuronal activity reduced and decrease consumption of ATP [14].

EE has profound effects on the developing and the adult brain, spanning from the molecular to the anatomical and behavioral level [15,16]. EE increases adult hippocampal neurogenesis by means of survival of new cells in the Dentate gyrus (DG) and involves cortical restructuring and affect different phases of the neurogenic process in distinct ways which improve spatial learning ability [16].

In adult animals, EE leads to better performance in various learning and memory tasks like the Morris-water-maze, the novel object recognition task and fear-conditioning task [17].

EE is also capable of delaying the progression and reducing provoked deficits of various neurological pathologies, including neurodegenerative diseases and stroke [18]. This is possibly due to increased levels of BDNF [19,20] and insulin-like growth factor 1 (IGF-1) [21], enhanced maturation of the inhibitory GABAergic system and accelerated CRE/CREB (cAMP response element-binding protein)-mediated gene expression [19].

In the adult rodent visual cortex, EE increase levels of BDNF (Brain derived neurotrophic factor) [22] and serotonin. Decrease GABA (Gamma amino butyric acid) levels and release [23] and number of GAD67+ interneurons [22,24].

Moreover, EE also increase levels of histone acetylation in the hippocampus and neocortex [25]. Rather, EE exposure actually converses already established long term potentiation (LTP) thus affects dendritic spine density, synaptic proteins receptors expression as well as expression of neurotrophins [26].

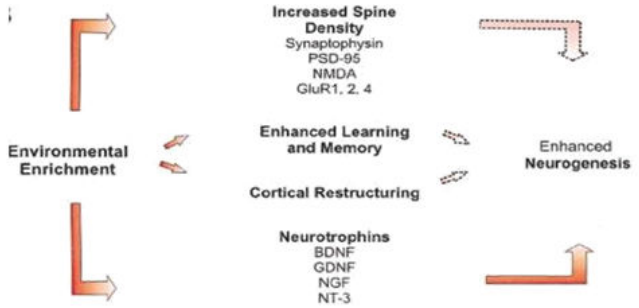

Figure 1: Effect of environmental enrichment on enhanced learning and memory & neurogenesis.

Sleep Deprivation and Rehabilitation (Recovery Sleep)

Recovery sleep induce by EE also induces various molecular and structural changes in the brain, contributing to the changes in neuronal functions and ultimate, in behavior. These mechanisms are thought to trigger EE-induced neural plasticity. Social contact and play behavior is important for normal development. The enriched social housing condition has compensated for the adverse effects of SD. Recovery sleep or rehabilitation by an enriched environment helps in removal of toxic by-products of wakefulness and redirects the regenerative power of sleep [27,28].

Effect of Recovery Sleep on Sleep Deprivation Induced Neurodegeneration

The harmful cellular consequences of prolonged waking may result from excitotoxicity and oxidative mechanisms which sensitize the brain to neurodegeneration [29,30]. Morrisey et al. (2003) reported that SD led to decreased brain mass, an increase in expression of apoptotic proteins in the cerebral cortex and, subsequently changes in behavior of adults [31]. EE induced recovery sleep improves neuronal survival, enhances neurogenesis and decreases apoptotic cell death. The survival-promoting effect of enrichment is expressed independently of the cell lineage, resulting in a net increase in both neuronal and glial cells in the dentate gyrus, although proportionally most of these new cells are neurons [32]. Shehata and Rizk reported that the recovery sleep led to ameliorative effects on cognition especially on memory and learning in 3 days sleep deprived rats. This might be due to the regenerative effects of sleep [28]. Wu et al. (2008) showed that the 24 hours of sleep could not reversed the deterioration caused by SD in the pre-frontal cortex, BAX (Bcl-2-associated X protein or a proapoptotic protein), Bcl-2 and the Bcl-2/BAX ratio not returning to basal levels. A possible explanation of this result is that effects of SD on the prefrontal cortex are long-lasting and more time is required for complete recovery [33].

Montes-Rodrı´guez et al. reported that the Bcl-2/BAX ratio increases during recovery sleep following SD and showed that the hippocampus seems to benefit from sleep [34]. An earlier study on p53 and Bcl-2 protein levels (pro- and anti-apoptosis proteins, respectively) after 6 hours of sleep deprivation and 2 hours of post-deprivation sleep (PDS) in the rat hypothalamus revealed an increase in Bcl-2 and p53 after SD and after PDS, the high levels of p53 and Bcl-2 being preserved [35].

Effect of Recovery Sleep on Neurogenesis

Sleep loss is reported to inhibit neurogenesis and cell proliferation in hippocampus, processes involved in learning and memory [36]. Mirescu et al. (2006) found that SD reduces adult neurogenesis and cell proliferation in the hippocampus by elevations in Glucocorticoid level.

The survival of the newborn cells and their neuronal differentiation, appear to be stronger stimulated by environmental enrichment [37,38]. In support of this explanation, previous studies showed that environmental enrichment promote hippocampal neurogenesis and may even decrease or reverse earlier brain deficits [18,39]. Study also suggested that 4 weeks of sleep restriction did not appear to affect the differentiation of new cells into neurons as double cortin (DCX) labeling in the outer granule cell layer (GCL) and subgranular zone (SGZ) of the DG did not differ between the control and sleep restricted groups. However, data showed that recovery sleep caused a significant increment in cell proliferation in the SGZ [40]. Exposure of animals to an EE led to enhanced neurogenesis specifically in the hippocampus and showed improvement in performance of several learning tasks [32]. One study concluded that in addition to increased neurogenesis by enrichment, enhanced synaptogenesis has also been observed in the CA3 and CA1 areas of the dentate gyrus in hippocampus. Hence it is proved that EE enhances proliferation, survival and maturation of neuronal cells, leading to improved cognition [33,34].

EE further modifies the expression of several enzymes, growth factors and transcription factors that are involved in the stimulation of neural stem cells (NSCs). Enhanced neurogenesis associates with improved synaptic plasticity and memory [41]. Hence, approaches aimed towards a better understanding of the modulation and control of neurogenesis, e.g. using peripheral or environmental factors, could have important clinical benefits in sleep disorders.

Effect of Recovery Sleep on Nitrergic Neurotransmitter Level

Sleep homeostasis is the process by which recovery sleep is spawned by prolonged wakefulness. Sleep loss, induced by prolonged wakefulness, produces a decline in cognitive and motor performance, mood disturbances, memory deficits and effects on immune function [42]. These effects are restored by recovery sleep, which is characterized by extension and intensification of both non-rapid eye movement (NREM) and rapid eye movement (REM) components. The possible role of nitric oxide (NO) in the regulation of behavioral state and specifically in the induction of recovery sleep suggesting that NO may have a role as a sleep facilitating agent. Neuronal NO neurotransmitter produced by inducible nitric oxide synthase (iNOS) is an important homeostatic factor in promoting recovery sleep after SD [43]. nNOS is co-localized with acetylcholine (ACh) in most of the basal forebrain (BF) nuclei, as well as in the laterodorsal tegmental (LDT) and pedunculopontine tegmental (PPT) nuclei that project to the BF and is involved in the regulation of the sleep–wake cycle. Study conducted in male rats assigned to EE for 1 year, showed that NO production decreased by 47% in hippocampal submitochondrial membranes of EE rats as compared with control animals [44]. The EE-induced structural and functional changes which include increase cell proliferation, and enhance the number and stability of synapses, occur through molecular cascades that include neurotransmitter levels, improved expression of regulatory proteins and increases in neurotrophic factor that promote neurotransmitter release, [45].

Effect of Recovery Sleep on Cholinergic Neurotransmitter Level

The neurodegeneration caused by SD may spread throughout the brain or affect prevalently specific types of neurons such as the cholinergic neurons. EE also reduces the effects of stress on acetylcholine concentrations. Studies suggested that EE increases the acetylcholine level thus reduces the reactivity of the cholinergic system to stress in the prefrontal cortex [46]. Levels of other neurotransmitters also increase following EE which are associated with synaptic plasticity [47]. EE-induced changes in neurotransmitter levels and excitatory activity also shifts following EE housing, due to an enhanced expression of AMPA and NMDA receptors with increase in hippocampal extracellular glutamate levels [46]. The effects of EE on the increase of acetylcholine in the pre-frontal cortex (PFC) could lead to differences in behavioral parameters such as consolidation of aversive memories and working memory [48].

Effect of Recovery Sleep on Sleep Deprivation Induced Behavioral Changes

Adults with chronic sleep loss report excess mental distress, depressive symptoms, anxiety, and alcohol use [49]. SD is being considered a trait marker for predicting anxiety. Anxiety has been recognized as one of the most important neurobehavioral consequences of rapid eye movement (REM) in sleep deprivation and in total SD (both REM+NREM) [50]. The mechanistic approach to SD induced anxiety is oxidative stress, nitric oxide (NO) stress, neuroinflammation as well as cholinergic signaling.

ROS production and clearance by endogenous antioxidant defense system [51]. The mechanism by which SD induces anxiety may be hypothesized as being linked with elevated oxidative stress in sleep-deprived subjects. Early studies in animals showed that the enhanced stimulation of recovery sleep induces by enriched environment produces many extraordinary benefits at anatomical, molecular as well as at behavioral levels. Exposure to an enriched environment, providing more opportunity for learning and social interaction than standard laboratory living conditions, has been shown to enhance behavioural performance in various learning tasks [52]. One study concluded that the EE mice showed decreased anxiety-like behavior and higher activity, revealed by the increased number of entries and by a greater percentage of time spent into the open arms of the elevated plus maze in comparison to standard animals. EE reduces fearfulness, as suggested by reduction of defecation in open field tests [53]. At the neurochemical level, earlier study Brenes et al., showed that overall 1 month exposure of EE was enough to produce strong behavioral and neurochemical effects. Social isolation increase 5-HT or serotonin turnover without affecting the tissue levels of 5-HT and norepinephrine (NE), a stress hormone in rats [54]. Nitric oxide synthase (NOS) enzyme is also involved in the regulation of anxiety, sleep and aggressive behavior.

Effect of Recovery Sleep on Cognitive Performance

Many studies have shown that acute sleep deprivation affects cognitive performance and emotionality. Previous experimental studies in healthy human subjects showed that successive nights of restricted sleep resulted in a gradually accruing decline in cognitive function [55]. Another study conducted by Franzen et al. compared a group of 15 healthy, young human adults following one night of sleep

deprivation with 14 who had normal sleep and concluded that sleep deprivation led to performance and mood deficits [56]. Study by Lim and Dinges suggested that sleep deprivation leads to a general slowing in response time, an increase in incorrect responses, and time-on task effect. Sustained attention deficits are responsible for many of the performance deficits in memory and executive functioning tasks following sleep deprivation [57].

The recovery processes of cognitive deficits after sleep loss are still obscure. Recovery sleep is different from normal sleep. Evidence suggested that one sleep period (at least eight hours) can reverse the adverse effects of total SD on cognition [58]. After chronic partial sleep restriction, it seems to take longer the recovery process of cognitive functioning than after acute total SD. One study observed that after one week of sleep restriction, three 8 h recovery nights were not enough to restore performance even in the group that spent 7 hrs in bed [59]. Thus concluded that the brain adapted to a stressful condition, during mild and moderate chronic partial SD, yet at a reduced level to maintain performance in humans. This adaptation process was obviously so challenging that it postponed the restoration of normal functioning. One recovery night is enough to restore cognitive performance and daytime sleepiness deficits induced by acute or chronic sleep deprivation [60]. A study investigating recovery after a period of chronic sleep restriction suggested that a single recovery night of up to 10 hrs time in bed is insufficient for some behavioral functions to return to prerestriction levels and deficits were reversed by repeated nights of recovery sleep [61]. Rehabilitation in traumatic brain injury (TBI) patients based on EE principles results in improved cognitive and motor skills [62]. A number of studies have also shown that by increasing the duration and intensity of exposure to rehabilitative therapy results in improved recovery times.

Conclusion

"Sleep is in essential, food for the brain. Insufficient sleep can be harmful, even life threatening. Sleep is thus an essential element, in learning and memory which allows us to perform critical daily functions at peak optimization when obtaining the correct amount. Sleep is important because it has a determining role in mental and physical health of individual, along with quality of life. In conclusion, sleep deprivation is a biological stress condition for the brain. All physiological and neurological changes due to SD ultimately lead to physical/cellular stress or oxidative stress, a condition which is a major cause of neurodegeneration [63]. SD cause hippocampal volume to be reduced because of neuronal cell death, diminished arborization in dendrites, slowed neurogenesis and a decreased number of glial cells.

An enriched environment (EE) which is a complex combination of social, cognitive, and physical stimulation has shown improvement in learning and memory in rodents housing in an EE. In particular, changes in neurotransmitter content, gliogenesis, synaptic plasticity and dendritic spine growth, increased brain weight, as well as up regulation of neurotransmitters, neurotrophin levels and adult hippocampal neurogenesis have been associated with cognitive enhancement.

By providing the environment necessary for neuronal maintenance and repair, it has been proposed that recovery sleep with novel and complex multisensory environments should result in enhancement in neural plasticity as well as various neurological and behavioral changes also occur. Current body of literature on the effects of rehabilitation by means of recovery sleep in neurological disease indicates that Environmental Enrichment represents significant therapeutic potential, on its own and in combination with pharmacological treatments. This is by inducing neuroprotective mechanisms and behavioral outcomes underlying molecular mechanisms of experience-induced plasticity that possibly can be used to identify new therapeutic targets.

Competing Interests

The authors declare that they have no competing interests.

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