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A Review of Protective Effects of Exercise on Cognitive Impairments Induced by Sleep Deprivation in Female Rats

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Abstract

Sleep is an important factor in memory consolidation and brain health. In addition, sleep disorder is a common complaint among females in comparison with males. In menopausal females, to relieve sleep disturbances and other menopausal symptoms, hormone therapy may be used. Furthermore, although estrogen had helpful effects on the brain performance, hormone replacement therapy augmented unfavorable cardiovascular and oncological side effects. It is implied that exercise is a powerful non-pharmacological intervention that can develop the cognitive performances. The current study used the behavioral, physiological, and molecular evidence supporting these views.

Keywords: Sleep Deprivation, Physical Exercise, Cognitive Function, Female Rat

1. Introduction and Statement of the Problem

Similar to other physiological functions, sleep regulation is carried out by the circadian clock in the hypothalamus. Sleep is characterized by 2 main phases: Non-rapid-eye movement (NREM) and sleep pursued by rapid-eye movement (REM) sleep. Sleep plays a vital role in health and performance. Many people diminish the amount of sleep time for business or lifestyle reasons in the modernized society. Evidence from experimental researches in humans indicate that sleep loss (less than 7 to 8 hours of sleep each night) causes significant impairment in cardiovascular, immune, endocrine and cognitive performances (1, 2). The national sleep foundation (NFS) reported that 7 to 8 hours of sleep is necessary for the best cognitive performance in adults (3). Other experiments confirmed the beneficial effects of sleep on declarative and non-declarative memory. It seems that sleep is the main factor in the acquisition and consolidation of memory (4, 5). Therefore, sleep deprivation (SD) impairs spatial (6, 7), emotional (8), and working memories (9), and augments anxiety like behaviors (10). As a result, hippocampus is very sensitive to sleep loss (11, 12). Accordingly, sleep deprivation negatively impacts long-term potentiation (12, 13), which is established as a form of synaptic plasticity (14, 15). Other studies demonstrated that generation and preservation of long-term potentiating (LTP) and spatial learning and memory are impaired by sleep deprivation. Sleep deprivation also decreases trophic factors such as brain derived neurotrophic factors (BDNF) level in the hippocampus of male (16) and female (6, 13, 17-19) rats.

It seems that cognitive functions (20), quality, and pattern of sleep (21) are different in the 2 genders. On the whole, hormonal factors -particularly estrogen levels- can change sleep patterns (22). It is also noticeable that changes in cognitive performance and sleep pattern and quality are often associated with sex hormones (23, 24). These findings highlight the importance of sex hormones in sleep regulation in the menopause period in females who indicate low levels of circulating estrogen (25) and are more sensitive to deleterious effects of sleep deficit on cognitive function (26).

Sleep disturbances are more common among females in comparison with males. Additionally, disturbed sleep is a more frequent compliant of menopausal and post-menopausal females (2, 25).

Additionally, regardless of the helpful effects of sexual hormones on the brain health, hormone replacement therapy has cardiovascular and oncological side effects (27); there is conspicuous concentration to develop helpful therapeutic methods to improve deteriorations associated with sleep deprivation.

The positive effects of physical activity on various physiological systems such as the nervous system and brain health are well displayed (28). Exercise can enhance cognitive performance and cell proliferation in the hippocampus (29).

Physical activity can develop some forms of synaptic plasticity such as LTP (28) and this protocol can also increase the level of BDNF (30).

Additionally, exercise can preserve memory impair-

ments (6) and improve LTP (13) in neurodegenerative diseases and estrogen deprivation periods (31).Other investigations revealed that regular activity can prevent the SD-induced impairments of cognitive function, synaptic plasticity, and signaling molecules in the hippocampus of male (16) and female rats (6, 13, 18, 19).

Given the conflicting effects of SD and regular physical activity on cognitive performances, it is rational to recommend that preconditioning the brain with regular exercise could compensate or weaken the harmful effects of SD on learning and memory. Specifically, this review was designed to assess the effects of physical exercise on cognitive impairments associated with SD in female rats.

2. Sleep, Memory, and Synaptic Plasticity

Several studies established that sleep had valuable effects on declarative and procedural memory in various tasks. During sleep, earlier encoded memory traces are reactivated and finally consolidated in the neocortex as a result of certain neuromodulators (eg, neurotransmitters) and cellular processes (eg, gene expression and protein translation). Several literature support a long-term integrative or consolidated function for different stages of sleep in newly obtained information (32, 33).

3. Modified Multiple Platform Paradigm

Sleep deprivation is accomplished by different techniques. One of these methods is modified multiple platform also recognized as the water tank or columns-in-water or inverted flowerpot model. Even though this method is well-organized in suppressing about 95% of REM sleep, it can also intervene with NREM sleep (34). As a result, the mentioned technique was based on a feature of REM sleep as muscle atonia (35). However, the fact that animals are restricted to the single platform introduces isolation stress as a confounding factor. Thereafter, the multiple platforms method was developed to alleviate movement restriction and social isolation associated with the single flowerpot method, thereby allowing the animals to move among several platforms. Later, the multiple platform technique was extended into the less disturbing modified multiple platform process, which allows animals from the same cage to experience SD together (Figure 1). The novel modified multiple platform diminishes psychosocial, immobilization, and separation stress as confounders often observed in the previous flowerpot models (34-36).

4. Sleep Deprivation and Cognitive Disorders

The chronic lack of sleep and sleep disorders became one of the typical features of the society. An ample body of evidence confirms a prominent relationship between SD and memory destruction both in animals and humans in different paradigms (7, 37, 38). Several experiments established the significant correlation between REM sleep and cognitive performances in male and female animals. Animals that experienced SD indicated significant cognitive impairments in various paradigms such as radial ram water maze (16), Morris water maze (MWM) (6, 17, 19), and the plus-maze discriminative avoidance task (39). The negative effects of SD on emotional memory of mice were previously recognized (8). The ability of mice to retain novel information and consolidate memory was interrupted by SD (40). Based on the results of previous studies, it seems that ovariectomized (OVX) female rats are more susceptible than intact animals to the harmful effects of SD on cognitive functions (6, 13, 18, 19). Additionally, these finding are compatible with those of human studies indicating that menopausal females were susceptible to negative effects of sleep loss (41). However, females in menopause period are more susceptible to the deleterious effects of poor sleep on cognitive performances (25, 42).

The results of the studies imply that sex hormones have strong neuroprotective functions against different neuronal and brain injuries (41, 43, 44), though the mechanism of occurrence is not completely understood.

Moreover, LTP is impaired after various periods of SD (13). The negative effect of SD on synaptic plasticity is thought to be a result of the fundamental harmful alterations in intracellular signaling molecules and receptors such as NMDA (N-Methyl-D-aspartic acid or N-Methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors (9, 45). For example, NMDA receptors that are important for the generation of LTP indicated harmful changes in receptor subunit formation and modulation after 24 hours of REM-SD (45). Another study indicated that phosphorylation and membrane trafficking of hippocampal glutamate AMPA receptors, which are critical in initiating synaptic plasticity, impaired after 12 hours of SD (9). Molecular studies also show that 8, 24, and 48 hours of SD can impair the expression of key signaling molecules and growth factors (eg, MAPK, CREB, and BDNF) related in LTP and cognitive function in the hippocampus (16, 46-48). Indeed, the reduced cognitive functions generated by sleep loss and/or business factors are approved as a dominant popular health and safety topics with abundant economic and social charges (1).

The results of the current experiment indicated that induction and maintenance of LTP in the hippocampus of

Figure 1. Multiple Platform Apparatus

all female rats impaired after 72 hours of SD, but ovariectomized group exhibited more deficiency, compared with the intact female animals; although this difference was insignificant (13).

Some human studies reported the augmented vulnerability of females during menopause to the harmful impacts of sleep deficits on psychological (49) and cognitive functions and brain health (50). The effects of estrogen on hippocampal function were further approved by experiments indicating augmented dendritic spine density, phosphorylation, and levels of NMDA receptor, as well as a raise in the induction of LTP in the hippocampus of female rats during pro-estrus period of estrous phase (51, 52). The estrogen loss was ultimately suggested as the fundamental candidate for mediating the higher vulnerability of OVX animals to the negative impacts of sleep deficits on cognition, brain health, and synaptic plasticity.

Additionally, previous findings also showed that OVX rats were more sensitive than intact animals to the harmful effect of sleep loss on BDNF levels (18). In the central nervous system (CNS), estrogen has widespread and different interactions with growth factors (53). The putative estrogen-sensitive response element (ERE) in the BDNF gene caused many researchers to propose that the regulation of BDNF expression in the CNS may be achieved through estrogen. Therefore, BDNF is considered as a main mediator of estrogen effects on cognitive function and hippocampal physiology with potential neuroprotective properties (54).

5. Exercise Recovers Cognitive Impairments in the Sleep-Deprived Female Rats

Physical exercise is thought to have useful impacts on cognitive performance. Several documents indicate that physical exercise can compensate deteriorations associated with SD in short- and long-term memories in male (16, 55) and female animals (6, 19). These data suggest that the helpful effects of regular activity on cognitive deficits caused by SD may be mediated by BDNF and other signaling molecules in the hippocampus.

Previous results indicated that 72 hours SD can impair the spatial learning of the OVX rats and spatial memory of both OVX and intact female animals (6, 56). Therefore, pre- and post-learning sleep deprivations also disrupt the short-term and long-term memory in female animals (6, 19). Nevertheless, animals that underwent regular treadmill exercise before SD had a recovered function in MWM test than the sleep-deprived rats. The beneficial effect of regular exercise was outstanding in OVX rats and the rats that did exercise before SD indicated an increased acquisition rate than SD group (6, 19).

It is demonstrated that regular exercise has constructive effects on the cognitive failure associated with aging (57). Regular activities can also promote cognitive performance in neurodegenerative diseases such as the Alzheimer disease (58, 59) and brain ischemia (60).

Although it is implied that physical activity recovers cognitive distraction in the sleep-deprived animals, at the same time, the effects of physical activity on cognitive functions is controversial. The results of some studies suggest that exercise can protect the brain during sleep deprivation or other neurodegenerative diseases (16, 55). However, some findings indicated that neither intentional nor involuntary exercises developed cognitive performance, and were not helpful in learning and retention in different hippocampal functions in normal experimental animals (61-65). Previously, it was indicated that voluntary exercise can promote the cell propagation in hippocampus and improve spatial navigation and aversive memory problems in the estrogen-deprived animals (29). These incompatible data may be due to some differences such as length and time of exercise training, and type and intensity of the experiment used. In addition, such different findings may be

due to the diversity in age and strain of the examined animals.

6. Exercise Prevents Synaptic Plasticity Impairments Induced by Sleep Deprivation

The positive effects of regular exercise on deleterious behavioral, synaptic, and molecular problems caused by sleep loss were shown in several studies (6, 13, 16, 18). These experimental studies demonstrated that the advantageous influences of regular activity at the cellular level were possibly as a result of its potential to augment the generation of BDNF and other signaling molecules in the sleep-deprived animals.

However, in the previous studies, treadmill exercise could compensate induction and maintenance of LTP deficits induced by sleep deprivation in the hippocampus of female (13) and male (16) rats. In addition, these results in a treadmill running model showed that exercise training alone had no meaningful effects on the LTP induction in normal animals (13). These findings support the claim that forced exercise may limit its capability to improve only in the existence of cognitive deficits. These investigations revealed that the production of BDNF and other signaling molecules, as a basic molecular mechanism of brain plasticity, increased in the sleep-deprived male rats that did exercise (16, 55).

However, it is extensively reported that running exercise alleviates different ischemic brain injury; facilitates recovery from injury, and raises protection against brain insult (60, 66), though the underlying mechanisms are poorly understood. These benefits are best delineated with respect to the promotion of neurotrophic factors expression such as BDNF (30). Although some exercise interventions indicated the significant promotion of cognitive function, learning, and memory function, and brain health (28, 63, 66-68), other studies revealed the lack of improvement of cognitive functions by exercise training (16, 55, 69). This disagreement may be due to the differences in the duration of training, type of activity, and intensity of the accomplished training exercises.

7. Effect of Regular Exercise and/or Sleep Deprivation on BDNF Levels in the Hippocampus of Female Rats

Data from molecular assays showed that hippocampal BDNF protein levels and mRNA expression of OVX female animals was decreased by sleep deprivation, meanwhile sleep-deprived animals that did exercise had higher hippocampal expression of mRNA and protein levels of BDNF (18). In addition, other experiments revealed that exercise training reversed deleterious alternations of signaling molecules such as BDNF in the hippocampus of sleep-deprived male rats (16, 55).

It was previously indicated that estrogen replacement therapy during postmenopausal in females can restrict the lessening of cognitive performance (70) and can diminish the danger of Alzheimer disease (71). Moreover ovarian steroid hormones increase the levels of BDNF protein and mRNA expression (54). Another document revealed that variations in emotion, sleep, as well as general, physical, and mental health during menopause in females were not considerable (72).

It is well documented that the function of BDNF in synaptic plasticity might be the main factor for protecting neural plasticity and disease support at the aging period and in neurodegenerative disorders (73). It is assumed that the correlation among steroid hormones, regular activity, and hippocampal BDNF level is possibly an important factor to defend brain healthiness (74).

Furthermore, physical exercise could avoid the diminishing effect of SD on BDNF level in the OVX female animals, although this running protocol did not influence the mRNA and protein levels of BDNF in the hippocampus of normal animals that did exercise (18). It was in agreement with other findings that demonstrated the lack of modified levels of hippocampal BDNF in groups that did exercise (69). These data support the notion that perhaps involuntary exercise training applies beneficial effects on insults or deteriorations such as sleep deficits, brain ischemia, and neurodegenerative diseases.

Therefore, several findings indicated that both voluntary and involuntary running can amplify the hippocampal trophic factor and other signaling molecules (16, 28).

Results of investigations about the effect of BDNF function on hippocampus performances generated inconsistent results. It is indicated that brain-derived neurotrophic factors play a main role in the functions associated with hippocampus (75, 76). On the contrary, other studies revealed that central application of BDNF did not improve the acquisition rate of spatial learning-damaged rats (77). Therefore, difference in techniques, including the duration and kind of regular activity and experimental procedure might cause diverse results.

8. Conclusions

In conclusion,

1) Evidence indicates that involuntary running can diminish SD-caused deficits of cognitive functions and synaptic plasticity in the male and female animals.

2) Molecular data indicated that physical activity used a defensive effect against the functions associated with hippocampus and synaptic plasticity destructions induced by sleep deprivation maybe by increasing BDNF protein, mRNA expression, and other signaling molecules in the hippocampus of OVX female rats.

Footnote

Conflict of Interest: The author declared no conflict of interest.

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